Multicomponent reactions, applications in medicinal chemistry & new modalities in drug discovery

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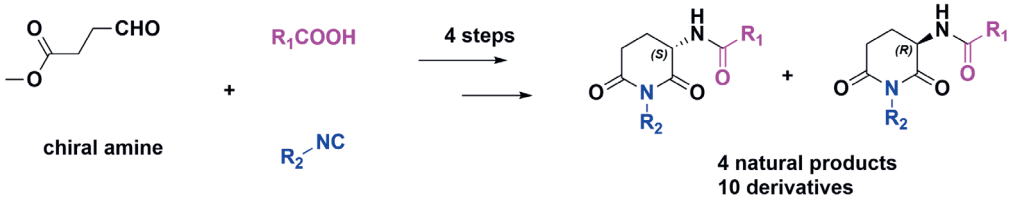
CHAPTER 3

GLUTARIMIDE ALKALOIDS THROUGH MULTICOMPONENT REACTION CHEMISTRY



This chapter is published

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ABSTRACT

A concise four step synthetic route for glutarimide alkaloids of high biological interest is presented. The scaffold is accessed via an Ugi four component reaction, hereby introducing two points of variation. This is followed by a hydrolysis, a cyclization under mild conditions and an amine deprotection. The diastereomers of the cyclized intermediate can be easily separated, thus leading to optically pure alkaloids. By this route, four natural products and ten derivatives were synthesized. The scope and limitations of the synthetic methodology are investigated.

INTRODUCTION

The glutarimide moiety (2,6-piperidinedione) is present in a number of natural product scaffolds and is linked to diverse biological activities. In medicinal chemistry, the glutarimide scaffold is present in derivatives with antibiotic,[1] antiviral,[2,3] anti-inflammatory[4] and neuroregenerative properties.[5] Glutarimide – containing polyketides have shown cell migration inhibitory activity,[6] and glutarimide macroketones are effective against cancer metastasis.[7]

Glutarimide alkaloids are an important class of natural products. The scaffold is present in the structure of julocrotine, which has shown antiproliferative effects in *in vitro* tests against the promastigote and amastigote forms of *Leishmania amazonensis*.[8]

The structure of julocrotine was elucidated in 1961 with a series of degradation reactions[9] and a report in 1974 showed the synthesis of a lower homologue using harsh conditions.[10] In 2011, a six step synthesis starting from *L*-glutamic acid was described.[11] Shortly afterwards, a four-step synthesis was described starting from Cbz-glutamine.[12] In this case, the key amine intermediate was used as the amine component of an Ugi reaction, but with limited diversity. Moreover, a stereoselective synthesis for julocrotine and structurally related glutarimide alkaloids was reported based on Boc-*L*-glutamine. [13] (Figure 1)

Altogether, although the previously reported methodologies lead to the desired natural products, they are restricted to the synthesis of only one alkaloid and not allowing easily the synthesis of derivatives. However, the establishment of a convenient synthetic route for structurally related natural products and derivatives is important for future pharmacological studies, to evaluate the title compounds as a lead structure. Thus, we envisioned an efficient synthetic route with variation points, which was first established for the natural product julocrotine.

For this aim, we employed multicomponent reaction (MCR) chemistry, which allows the effective synthesis of complex scaffolds in a few steps having as starting point easily accessible and diverse building blocks. [14,15,16] Multicomponent reaction products are easily amenable and tolerate a significant amount of functional groups and by post-modifications can lead to diverse and complex scaffolds.[17,18]

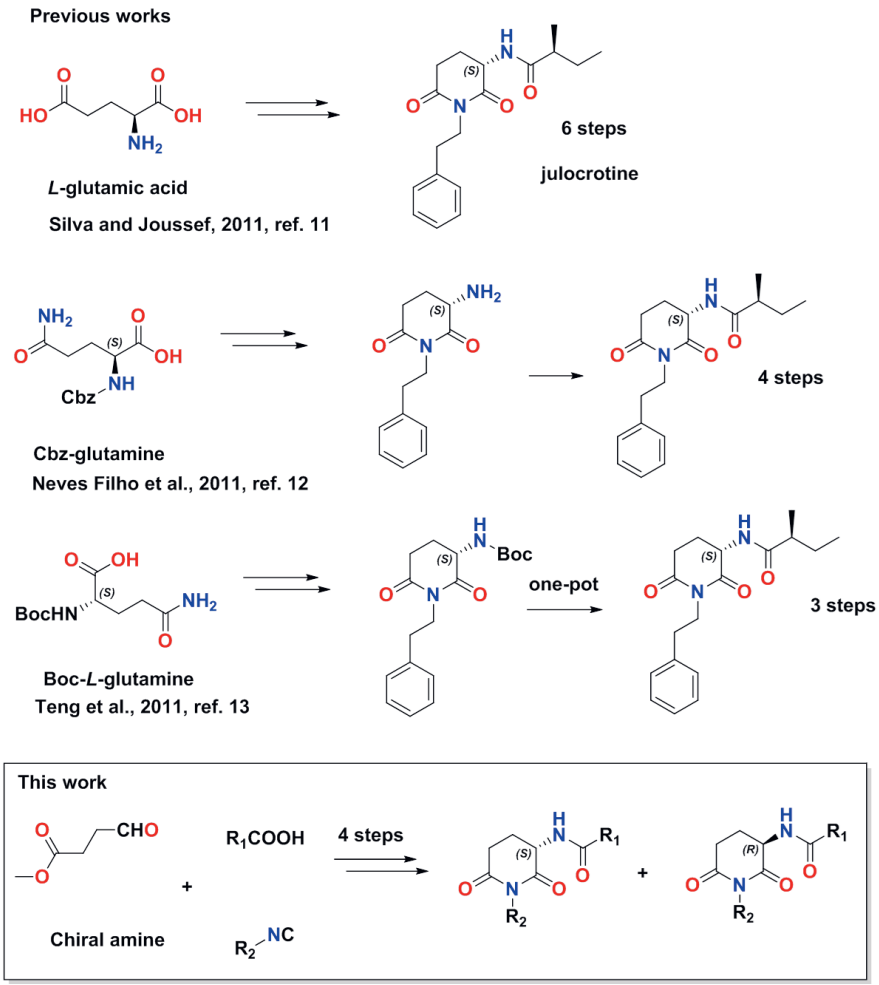
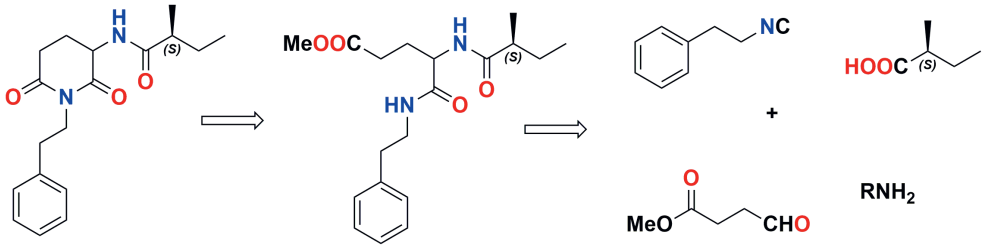


Figure 1. Previous works and current approach.

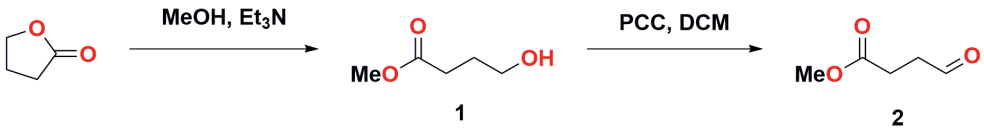
RESULTS AND DISCUSSION

Retrosynthetically, the glutarimide scaffold can be accessed via a 4-component Ugi reaction, followed by an intramolecular cyclization (Scheme 1).



Scheme 1. Retrosynthesis.

The aldehyde was synthesized in two steps by applying previously described conditions with slight modifications;[19,20,21] first the opening of γ-butyrolactone towards methyl 4-hydroxybutanoate, and then the oxidation to methyl 4-oxobutanoate (Scheme 2).



Scheme 2. Aldehyde synthesis.

We found that the use of pyridinium chlorochromate (PCC) resulted in much higher yields compared to the Swern oxidation. Oxidation by Dess-Martin periodinane led to lower yields than PCC and it was challenging to reproduce the same yields. Moreover, with the ring opening approach, followed by the oxidation with PCC, the aldehyde can be easily prepared at a scale of 3 grams.

(R)-(+)-1-(4-methoxyphenyl)-ethylamine was used as a chiral auxiliary which also can be easily deprotected on a later stage. The overall synthetic route was established as a mild four step synthesis starting from a four-component Ugi reaction. The following table (Table 1) summarizes our optimization attempts for the Ugi reaction.

Table 1. Optmiziation for the Ugi reaction.

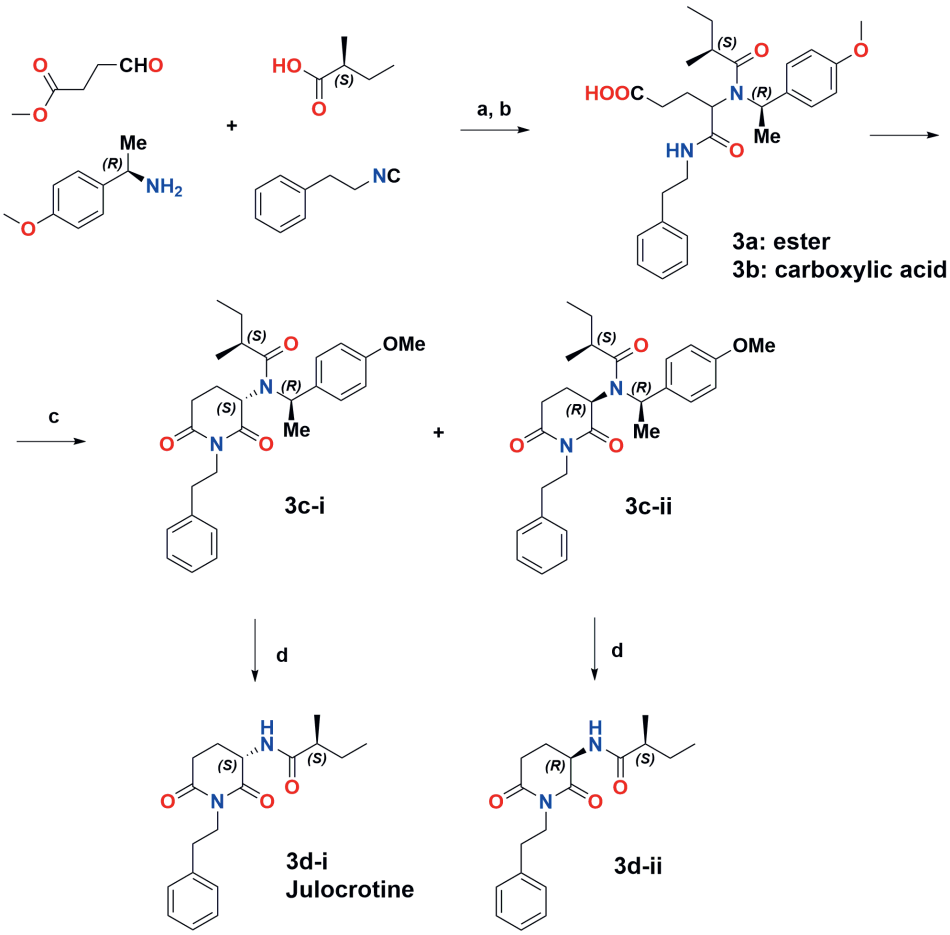
	Solvent	Concentration	Catalyst	Time, Heating	Yield[b]
1	MeOH	1M	-	rt, 24 h	15%
2	MeOH	1M	-	rt, 48 h	35%
3	TFE[a]	1M	-	rt, 24 h	38%
4	TFE	1M	$ZnCl_2$	rt, 24 h	24%
5	**TFE**	**1M**	**-**	**rt, 48 h**	**60%**
6	TFE	1M	-	MW,100°C, 1 h	12%
7	TFE	2M	-	rt, 24 h	36%

[a] 2,2,2-trifluoroethanol (TFE), [b] isolated yield after column chromatography

The standard Ugi solvent, methanol at room temperature overnight, gave only a low conversion of 15%. Prolonging the time at 48 h, increased the yield to 35%. An improvement was observed with the use of 2,2,2-trifluoroethanol (TFE) as solvent. However, the use of a Lewis acid (zinc chloride) as catalyst considerably reduced the yield. Remarkably, heating the reaction mixture in microwave conditions gave the lowest yield of only 12%. Changing the concentration from 1 M to 2 M, had almost no influence with yields of 38% and 36%, respectively. The optimal conditions turned out to be TFE, 1 M concentration, room temperature and 48 h reaction time. Under these conditions 60% product was isolated.

With the optimized conditions in hand for the Ugi reaction, we moved on to the next synthetic steps: an ester hydrolysis under basic conditions (95% yield), followed by the intramolecular cyclization with acetic anhydride and sodium acetate (74% yield for the diastereomeric mixture). In the last step, the amine protecting group is cleaved (Scheme 3).

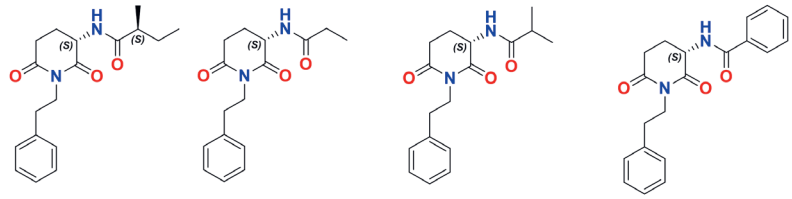
From the Ugi reaction, a new chiral center is introduced; thus diastereomers are formed. The diastereomers can be separated easily after the cyclization step by column chromatography (in **3c** the diastereomeric ratio was 3:2, after separation with column chromatography). In the last step, the cyclized products were deprotected separately to yield the natural julocrotine **3d-i** and its diastereomer **3d-ii**. The initial attempt to deprotect **3c-i** by hydrogenation on Pd/C was unsuccessful, but deprotection by refluxing with TFA resulted in quantitative yield of **3d-i**.



Scheme 3. Synthetic route for natural julocrotine. Conditions: (step 1) 2,2,2-trifluoroethanol (TFE), rt, 48 h, 1 M, (step 2) LiOH, MeOH – H_2O 2:1, rt, 5 h, (step 3) $(CH_3CO)_2O$, CH_3COONa, reflux, 2 h, separation of diastereomers by column chromatography, (step 4) TFA reflux, 24 h.

The pivotal question was the assignment of the stereochemistry for the final products. In order to determine the stereochemistry, a crystal structure was solved for one of the diastereomers in the cyclization step. This indicated that the isolated product (compound **3c-ii**) had (*R,R,S*) configuration. Thus, in order to obtain the major diastereomer with the correct stereochemistry, the synthesis was repeated with the *(S)*-(-)-4-methoxy-α-methylbenzylamine auxiliary. The optical rotations of the final product **3d-i** and **3d-ii** were the ultimate proof that the stereochemistry is maintained in the deprotection step and that the major product was the natural alkaloid julocrotine by using the *(S)*-(-)-4-methoxy-α-methylbenzylamine auxiliary.

Next we were keen to apply the same synthetic approach to the structurally related natural products crotonimides A, B and C. [13,22,23] For these three alkaloids the amino-component was the *(S)*-(-)-4-methoxy-α-methylbenzylamine auxiliary, whereas the carboxylic acids were propionic acid for crotonimide A, isobutyric acid for crotonimide B and benzoic acid for crotonimide C (Scheme 4).



julocrotine
3d-i

crotonimide A
4d-ii

crotonimide B
5d-ii

crotonimide C
6d-i

Scheme 4. Structures of julocrotine and crotonimides A, B, C.

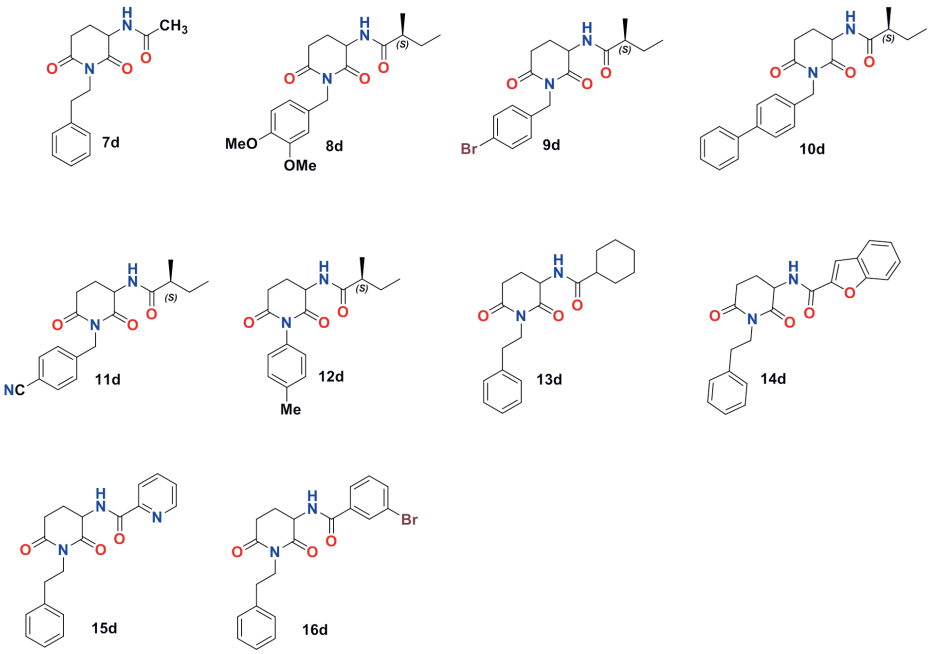
It is well-established that the Ugi reaction is not very stereoselective. However, it is noteworthy that the diastereomeric ratios (*S,S*) / (*R,S*) as determined by separation in the cyclization step varied significantly. Even the reverse of the ratio (*S,S*) / (*R,S*) of 4:5 and 3:2 was observed for crotonimide A and B. The greatest difference was observed for crotonimide C with a ratio (*S,S*) / (*R,S*) of 1:5. Thus the natural product in this case was the minor formed diastereomer (Table 2). Although the route is not diastereoselective, the four natural products could be synthesized with the same approach and the diastereomers were easily separated after the cyclisation step. Finally, optically pure compounds were obtained for the four natural products, which is an advantage for potential biological screening, since different enantiomers might cause different biological effects. To the best of our knowledge, this is the first report for the synthesis of both enantiomers for these three glutarimide alkaloids (crotonimides A, B and C).

Table 2. Isolated yields and diastereomeric ratios (step 3) for the natural products.

Natural product	Step 1[a]	Step 2[a]	Step 3[a][b]	Step 4[a]
julocrotine	60% **(3a)**	95% **(3b)**	74% (combined) **(3c-i):(3c-ii)** 2:3	96% **(3d-i)** 83% **(3d-ii)**
crotonimide A	52% **(4a)**	99% **(4b)**	41% (combined) **(4c-i):(4c-ii)** 5:4	82% **(4d-i)** 90% **(4d-ii)**
crotonimide B	52% **(5a)**	95% **(5b)**	53% (combined) **(5c-i):(5c-ii)** 2:3	90% **(5d-i)** 82% **(5d-i)**
crotonimide C	55% **(6a)**	85% **(6b)**	45% (combined) **(6c-i):(6c-ii)** 1:5	90% **(6d-i)** 93% **(6d-i)**

[a] isolated yields, [b] diastereomeric ratios were determined after separation with column chromatography.

Next, we went on with the synthesis of a small compound library in order to further explore the scope and limitations of this synthetic approach. The initial Ugi four-component reaction offers two points of variation: the carboxylic acid and the isocyanide component. The aldehyde was kept constant to afford six-membered glutarimides. To investigate the scope and limitation, 10 derivatives were synthesized by using the *(R)*-(+)-1-(4-methoxyphenyl)-ethylamine and varying either the carboxylic acid or the isocyanide (Scheme 5).



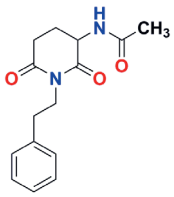
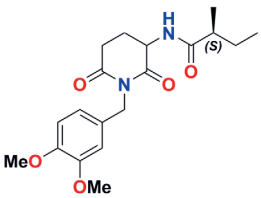
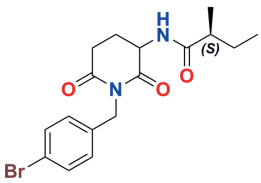
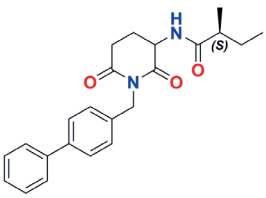
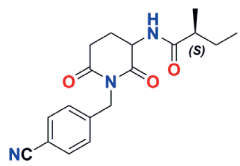
Scheme 5. Structures of the glutarimide natural product inspired library components.

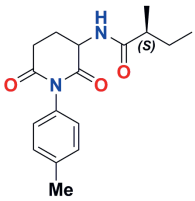
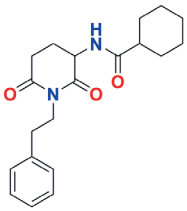
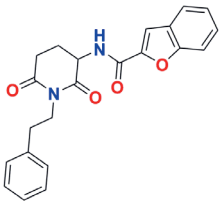
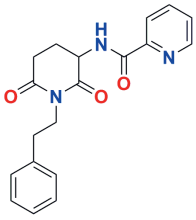
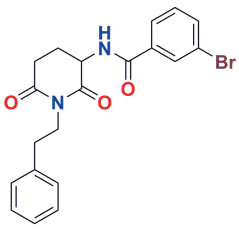
The cyclization products were deprotected as combined (*S* and *R* mixtures with unspecified ratio) or diastereomeric mixtures, although it would have been possible to separate the diastereomers in the cyclization step with column chromatography, if necessary for future biological screening.

The isolated yields for the Ugi reaction varied from 24% to 53% (Table 3). For the natural products **3a**, **4a**, **5a**, **6a** and derivatives **7a** and **13a**, which all had the phenyl-ethyl isocyanide and different aliphatic carboxylic acids (either linear or cyclic) the yields ranged from 52 to 60%. Derivatives **8a**, **9a**, **10a**, **11a** and **12a** based on (*S*)-(+)-2-methyl-butyric acid and variable isocyanides gave yields from 36 to 50%. The lowest yields in those cases were observed with 4-methyl-phenyl-isocyanide **12a** (36%) and the bulky 4-biphenyl-isocyanide **10a** (37%). Electron withdrawing groups on the benzyl isocyanide such as bromo for **9a** and cyano for **11a** resulted in 50% and 40% yield, respectively. The electron donating 3,4-dimethoxy group on the benzyl isocyanide of **8a** gave the desired product with 52% yield. The bigger variations were observed for the derivatives **14a**, **15a** and **16a**, which had the phenyl-ethyl isocyanide and aromatic carboxylic acids. The higher yield was observed with the 2-pyridine carboxylic acid **15a** (41%), whereas the 2-benzofuran **14a** and the meta-bromo-benzoic acid **16a** gave only 24% and 29% yields, respectively. In the hydrolysis step the yields ranged from quantitative to 65%, in the cases of derivatives **15b** (2-pyridine carboxylic acid) and **16b** (*meta*-bromo-benzoic acid). The yields in the cyclization step varied significantly from 17% to 94%. Regarding the carboxylic acid variations in the cyclization step, the yields

were moderate [benzofuran-2-carboxylic acid **14c** (46%), pyridine-2-carboxylic acid **15c** (55%), acetic acid **7c** (62%), cyclohexane-carboxylic acid **13c** 67%)], with the exception of *meta*-bromo-benzoic acid **16c** (17%). The isocyanide variation in the same step resulted in moderate yields in the cases of the 3,4-dimethoxy-benzyl-isocyanide **8c** (20%) and the 4-methyl-phenyl-isocyanide **12c** (31%). On the contrary, the yields were high in the cases of 4-bromo-benzyl-isocyanide **9c** (52%), 4-biphenyl-isocyanide **10c** (72%) and 4-cyano-phenyl-isocyanide **11c** (94%). The final acid-mediated deprotection was performed in high yields in all cases (70-98%).

Table 3. Isolated yields for derivatives.

Structure	Step 1[a]	Step 2[a]	Step 3[a][b]	Step 4[a][b]
	53% **(7a)**	98% **(7b)**	62% **(7c)**	85% **(7d)**
	52% **(8a)**	80% **(8b)**	20% **(8c)**	75% **(8d)**
	50% **(9a)**	78% **(9b)**	52% **(9c)**	98% **(9d)**
	37% **(10a)**	90% **(10b)**	72% **(10c)**	77% **(10d)**
	40% **(11a)**	86% **(11b)**	94% **(11c)**	70% **(11d)**

	36% **(12a)**	96% **(12b)**	31% **(12c)**	82% **(12d)**
	55% **(13a)**	82% **(13b)**	67% **(13c)**	90% **(13d)**
	24% **(14a)**	97% **(14b)**	46% **(14c)**	89% **(14d)**
	41% **(15a)**	71% **(15b)**	55% **(15c)**	85% **(15d)**
	29% **(16a)**	65% **(16b)**	17% **(16c)**	90% **(16d)**

[a] isolated yields, [b]stereoisomeric mixture (combined or diastereomeric mixtures)

Limitations of the methodology were noted in the cases of adamantyl- and indole substituents. The use of 1-adamantyl-isocyanide resulted in the Ugi and saponification products as expected. However, in the cyclization step only unreacted starting material was obtained, likely due to steric hindrance. Furthermore, the use of the indole moiety, either as carboxylic acid or isocyanide component, resulted into complicated reaction mixtures in the Ugi reactions. The obtained products could not be used further due to very low purity.

An interesting observation was done when using *meta*-bromo-benzoic acid. In the cyclization step only one diastereomer (**16c**) was observed (as indicated by NMR data), which was deprotected towards an enantiomer with optical rotation of [α]= +13.57 (c = 0.84, $CHCl_3$) (**16d**). Although the optical rotation and NMR data are not sufficient for determining the absolute configuration of the product, this unexpected result seems to be in agreement with the data from crotonimide C, where the again aromatic benzoic acid component induced a high ratio (*S*,*S*) /(*R*,*S*) of 1:5.

CONCLUSIONS

We have established a mild multicomponent synthetic approach for glutarimide alkaloids, allowing the straight forward synthesis of derivatives. The methodology was used for the successful synthesis of four optically pure natural products. The scope and limitations for a small library synthesis were examined and the stereochemistry was investigated. By our synthetic route, the biological evaluation of the glutarimide alkaloid scaffold will be significantly facilitated in the future.

REFERENCES

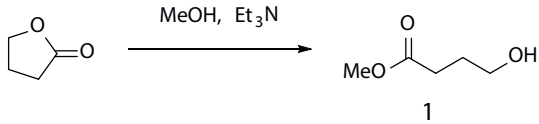
1. H.F. Guo, Y.H. Li, T. Zhang, S.Q. Wang, P.Z. Tao, Z.R. Li, *J. Antibiot.* **2009**, *62*, 639 – 642.
2. K.X. Chen, L. Nair, B. Vibulbhan, W. Yang, A. Arasappan, S.L. Bogen, S. Venkatraman, F. Bennett, W. Pan, M.L. Blackman, Al. Padilla, A. Prongay, K.C. Cheng, X. Tong, N.Y. Shih, F.G. Njoroge, *J. Med. Chem.* **2009**, *52*, 1370 –1379.
3. X.Y. Ji, Z.J. Zhong, S.T. Xue, S. Meng, W.Y. He, R.M. Gao, Y.H. Li, Z.R. Li, *Chem Pharm Bull* **2010**, *58*, 1436 –1441.
4. D.J. Fox, J. Reckless, S.G. Warren, D.J. Grainger, *J. Med. Chem.* **2002**, *45*, 360 – 370.
5. C. Christner, R. Wyrwa, S. Marsch, G. Küllertz, R. Thiericke, S. Grabley, D. Schumann, G. Fischer, *J. Med. Chem.* **1999**, *42*, 3615 – 3622.
6. S.R. Rajski, B. Shen, *Chembiochem* **2010**, *24,* 1951 – 1954.
7. L. Chen, S. Yang, J. Jakoncic, J.J. Zhang, X.Y. Huang, *Nature* **2010**, *464*, 1062 – 1066.
8. L.R. Guimarães, A.P. Rodrigues, P.S. Marinho, A.H. Muller, G.M. Guilhon, L.S. Santos, J.L. do Nascimento, E.O Silva, *Parasitol Res.* **2010**, *107,* 1075 – 1081
9. T. Nakano, C. Djerassi, R.A. Corral, O.O Orazi, *J. Org. Chem.* **1961**, *26*, 1184 – 1191.
10. K.L. Stuart, D. McNeill, J.P. Kuntney, G. Eingendorf, F.K. Klein, *Tetrahedron* **1973**, *29*, 4071 – 4075.
11. L.L. Silva, A.C. Joussef, *J. Nat. Prod.* **2011**, *74*, 1531 – 1534.
12. R.A. Neves Filho, B. Westermann, L.A. Wessjohann, *Beilstein J. Org. Chem.* **2011**, *7,* 1504 – 1507.
13. B. Teng, J. Zheng, H. Huang, P. Huang, *Chin. J. Chem.* **2011**, *29*, 1312 – 1318.
14. A. Dömling, *Chem. Rev.* **2006**, *106*, 17 – 89.
15. A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012,** *112*, 3083 – 3135.
16. T. Zarganis – Tzitzikas, A.L. Chandgude, A. Dömling,*Chem. Rec.* **2015**, *15*, 981 – 996.
17. G.Koopmanschap, E. Ruijter, R.V. Orru, *Beilstein J. Org. Chem.* **2014,** *10,* 544 – 598.
18. U.K. Sharma, N. Sharma, D. Vachhani, E.V. Van der Eycken *Chem. Soc. Rev.* **2015**, *44*, 1836 – 1860.
19. A. Ohashi, A. Satake, Y. Kobuke, *Bull. Chem. Soc. Jpn.* **2004**, *77,* 365 – 374.
20. P.M. Gannett, D.L. Nagel, P.J. Reilly, T. Lawson, J. Sharpe, B.Toth *J. Org. Chem.* **1988**, *53*, 1064 – 1071.
21. A.L. Gutman, A. Boltanski, *J. Chem. Soc. Perkin Trans. 1*, **1989**, *0,* 47 – 49
22. P.S Barbosa, A.S Abreu, E.F. Batista, G.N.S.P. Guilhon, A.H. Müller, M.S.P. Arruda, L.S. Santos, A.C. Arruda, R.S. Secco, *Biochem. Syst. Ecol.* **2007**, *35*, 887 – 890.
23. B. Ndunda, M.K. Langat, J.M. Wanjohi, J.O. Midiwo, L.O. Kerubo, *Planta Med.* **2013**, 79, 1762 – 1766.

EXPERIMENTAL SECTION

General experimental procedures

Procedures for the aldehyde synthesis

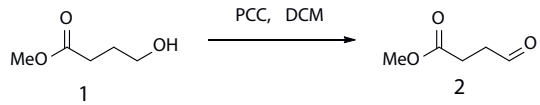
methyl 4-hydroxybutanoate[S1,S2] (1)



1

Gamma-butyrolactone (1 equiv., 34.8 mmol, 3 grams) was dissolved in 80 ml of methanol. At 0 °C triethylamine was added (6 equiv., 208.8 mmol, 29 ml). The reaction mixture was stirred at 0 °C for 30 min and then in room temperature (rt) overnight. The solvent was removed under reduced pressure and the residue was purified by flash filtration on silica (petroleum ether : ethyl acetate [0 to 100% EtOAc in PE] to obtain a light yellow liquid (3.66 grams). Mixture of product to starting material 7:3 (determined by NMR). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (t, *J* = 7.1 Hz, 0.57H, lactone), 3.49 (b, 1H), 3.43 (s, 3H), 3.37 (dd, *J* = 10.5, 6.2 Hz, 2H), 2.26 (t, *J* = 8.2 Hz, 0.59H, lactone), 2.18 (t, *J* = 7.4 Hz, 2H), 2.09 – 2.00 (m, 0.63H, lactone), 1.60 (ddd, *J* = 13.7, 7.4, 6.3 Hz, 2H).

methyl 4-oxobutanoate[S2,S3] (2)



1 2

Pyridinium chlorochromate (1.5 equiv., 33.2 mmol, 7.1 grams) was added in one portion in 88 ml of DCM (0.25 M) and was stirred at rt under $CaCl_2$ drying tube to form an orange suspension. Starting material (1 equiv., 22 mmol, 3.27 grams, mixture of alcohol : unreacted γ-butyrolactone 8:2) was dissolved in 5ml of DCM and added quickly in one portion under vigorous stirring at rt. The reaction mixture becomes immediately dark brown. The reaction was monitored by TLC (PE : EA 1:1 plus $KMnO_4$ staining). After 2 h the alcohol was fully consumed. In the reaction mixture diethylether (100ml) was added and the black gummy precipitate was separated by filtration on silica, with diethylether as eluent. Solvents were removed under reduced pressure to get a light yellow liquid (3.05 grams, mixture of product to unreacted γ-butyrolactone 7:3, ratio determined by NMR). The aldehyde was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 4.33 (t, *J* = 6.8 Hz, 0.67H, lactone), 3.67 (s, 3H), 2.79 (t, *J* = 6.3 Hz, 2H), 2.62 (t, *J* = 6.3 Hz, 2H), 2.47 (t, *J* = 8.0 Hz, 0.69H, lactone), 2.26 (t, *J* = 7.3 Hz, 0.61H, lactone).

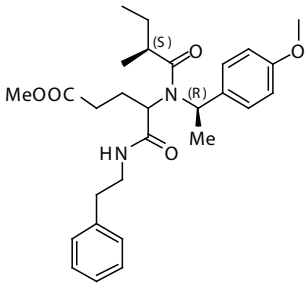
Procedure A (General procedure for the Ugi reaction): In a round bottom flask, 2,2,2-trifluoroethanol (TFE, 1 M) was added, followed by the addition of the aldehyde (1 equiv.) and the amine (1 equiv.). After 30 min of stirring in rt, the carboxylic acid (1 equiv.) and the isocyanide (1 equiv.) were added. The reaction mixture was stirred at rt for 48 h. Then, the solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography (eluent: PE – EA [0 to 100% EtOAc in PE]). For natural products, the scale was 4 mmol, whereas for derivatives the scale was 1.5 mmol.

Procedure B (General procedure for the hydrolysis): The Ugi product (1 equiv.) was dissolved at rt in a mixture of MeOH – H_2O (2:1, 10 ml for 1mmol of starting material). LiOH (1.5 equiv.) was added as solid. The reaction mixture was stirred at rt for 5 h. Then methanol was removed under reduced pressure. The residue was diluted with water (50 ml) and extracted with ethyl acetate (x2). The basic aqua phase was cooled in an ice-bath and was acidified with 2N HCl, followed by an extraction with ethyl acetate (50ml x 3). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

Procedure C (General procedure for the cyclization): The carboxylic acid (1 equiv.) was dissolved in acetic anhydride (5 ml for 1 mmol of starting material). Sodium acetate (1.2 equiv.) was added as solid. The reaction mixture was heated to reflux and the reaction was monitored by TLC PE:EA 1:1. After 2 h, it was allowed to reach rt. Then the reaction mixture was cooled in an ice-bath and water was added. Extraction with DCM (50ml x 2). The organic layers were dried over Na_2S0_4, filtered and the solvent was removed under reduced pressure. The dark brown residue was purified by column chromatography (PE:EA [0 to 100% EtOAc in PE]). For the four natural products, diastereomers were separated during the purification, whereas for the 10 derivatives no separation was attempted.

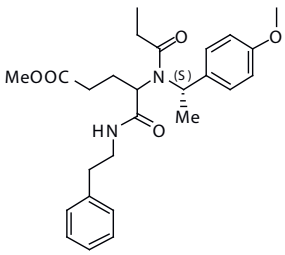
Procedure D (General procedure for the deprotection): The cyclized product was dissolved in TFA (for 1 mmol 10 ml). The reaction mixture was stirred at rt for 10 min and then overnight reflux under $CaCl_2$ drying tube. The reaction mixture turned red. After 24 h it was allowed to reach rt. Addition of 30 ml of DCM and evaporation under reduced pressure. The red residue was diluted with ethyl acetate (50ml) and was washed with sat. $NaHCO_3$ (50 ml x 3). The organic layer was dried over $MgSO_4$, filtered and solvent was removed under reduced pressure to get a brown residue, which was purified by column chromatography.

methyl 4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamido)-5-oxo-5-(phenethyl amino) pentanoate (3a)



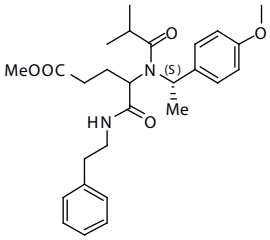
Obtained using procedure A, on 4 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 60% (2.40 mmol, 1158 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.39 (d, *J* = 8.6 Hz, 1H), 7.29- 7.27 (m, 3H), 7.23 – 7.18 (m, 5H), 7.17 – 7.12 (m, 5H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.91 – 6.85 (m, 3H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.19 – 5.08 (m, 2H), 3.81 (s,3H), 3.77 (s, 3H), 3.67 (s, 3H), 3.62 – 3.58 (m, 1H), 3.52 (s, 3H), 3.45 – 3.42 (m, 1H), 3.31 (dd, *J* = 13.0, 6.6 Hz, 3H), 2.82 – 2.79 (m, 1H), 2.69 – 2.57 (m, 6H), 2.55 – 2.45 (m, 1H), 2.38 (t, *J* = 7.3 Hz, 3H), 2.02 – 1.91 (m, 2H), 1.88 – 1.83 (m, 2H), 1.77 – 1.72 (m, 2H), 1.67 (d, *J* = 7.0 Hz, 3H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.47 – 1.40 (m, 2H), 1.19 – 1.14 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.97 – 0.86 (m, 8H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 178.4, 173.7, 173.6, 170.9, 170.0, 159.2, 159.1, 139.0, 138.9, 129.2, 128.7, 128.6, 128.4, 128.3, 126.5, 126.3, 114.6, 114.0, 58.7, 55.3, 55.2, 51.6, 51.4, 40.4, 40.3, 39.4, 39.2, 35.6, 35.2, 31.1, 27.7, 27.4, 25.6, 25.5, 18.1, 17.9, 17.3, 17.0, 12.4, 12.2. MS (ESI): *m/z* calcd for $C_{28}H_{38}N_2O_5$ $[M]^+$: 482.28 ; found $[M+H]^+$: 483.38; found $[M+Na]^+$: 505.36, HRMS (ESI): *m/z* calcd for $C_{28}H_{39}O_5N_2$ $[M+H]^+$: 483.28535; found 483.28537.

methyl 4-(N-((*S*)-1-(4-methoxyphenyl)ethyl)propionamido)-5-oxo-5-(phenethylamino) pentanoate (4a)



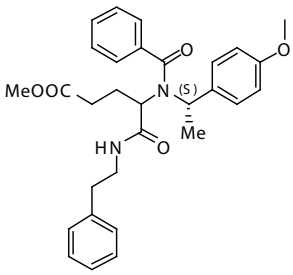
Obtained using procedure A, on 4 mmol scale, starting from *S*-(-)-1-(4-methoxy-phenyl)ethylamine; yield 52 % (2.08 mmol, 945 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.33 – 7.30 (m, 5H), 7.25 – 7.22 (m, 2H), 7.21 – 7.18 (m, 4H), 7.15 (d, *J* = 7.3 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 6.92 – 6.85 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.37 (b, 1H), 5.03 (ABq, *J* = 6.8 Hz, 2H), 3.77 (s, 6H), 3.66 (s, 6H), 3.68 – 3.58 (m, 2H), 3.48 – 3.41 (m, 2H), 3.06 (dd, *J* = 12.3, 6.2 Hz, 1H), 2.85 – 2.79 (m, 2H), 2.74 – 2.62 (m, 6H), 2.46 – 2.44 (m, 6H), 2.20 – 2.18 (m, 1H), 1.93 – 1.89 (m, 2H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.48-1.42 (m,3H), 1.23 – 1.09 (m, 6H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 175.1, 173.9, 170.6, 159.2, 139.3, 131.1, 129.1, 128.8, 128.7, 128.4, 128.3, 127.3, 126.4, 114.1, 114.0, 60.7, 58.0, 55.2, 51.5, 51.4, 40.3, 40.2, 35.5, 35.4, 31.2, 31.1, 28.3, 28.0, 25.7, 25.4, 21.6, 17.6, 9.5, 9.4. MS (ESI): *m/z* calcd for $C_{26}H_{34}N_2O_5$ $[M]^+$: 454.25; found $[M+H]^+$: 455.33; found $[M+Na]^+$: 477.31, HRMS (ESI): *m/z* calcd for $C_{26}H_{35}O_5N_2$ $[M+H]^+$: 455.25400; found 455.25409.

methyl 4-(N-((*S*)-1-(4-methoxyphenyl)ethyl)isobutyramido)-5-oxo-5-(phenethylamino)-pentanoate (5a)



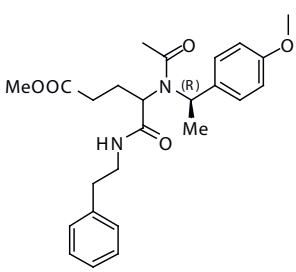
Obtained using procedure A, on 4 mmol scale, starting from *S*-(-)-1-(4-methoxy-phenyl)ethylamine; yield 52% (2.08 mmol, 975 mg), colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.40 (d, *J* = 8.5 Hz, 1H), 7.34 – 7.31 (m, 3H), 7.25 – 7.17 (m, 8H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.92 – 6.89 (m, 2H), 6.84 – 6.81 (m, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.11 (ABq, *J* = 6.8 Hz, 2H), 3.79 (s, 6H), 3.69 (s, 6H), 3.62 – 3.58 (m, 1H), 3.48 – 3.46 (m, 1H), 3.39 – 3.35 (m, 2H), 3.30 – 3.27 (m, 1H), 2.86 – 2.81 (m, 3H), 2.72 – 2.61 (m, 6H), 2.40 (t, *J* = 7.3 Hz, 4H), 2.01 – 1.85 (m, 2H), 1.68 (d, *J* = 7.0 Hz, 3H), 1.58- 1.52 (m, 3H), 1.21 (t, *J* = 7.0 Hz, 6H), 1.06 – 1.00 (m, 6H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 179.0, 178.8, 173.6, 172.8, 170.8, 170.4, 159.1, 159.0, 139.1, 138.9, 129.2, 128.7, 128.6, 128.4, 128.2, 126.7, 126.3, 114.6, 114.0, 60.6, 58.6, 55.3, 55.2, 51.6, 51.4, 40.8, 40.4, 35.5, 35.4, 32.2, 32.1, 31.04, 25.4, 20.5, 20.3, 19.8, 19.7, 19.5, 19.4, 18.4, 18.2. MS (ESI): *m/z* calcd for $C_{27}H_{36}N_2O_5$ $[M]^+$:468.26; found $[M+H]^+$: 469.36; found $[M+Na]^+$: 491.30, HRMS (ESI): *m/z* calcd for $C_{27}H_{37}O_5N_2$ $[M+H]^+$: 469.2697; found 469.2699.

methyl-4-(N-((*S*)-1-(4-methoxyphenyl)ethyl)benzamido)-5-oxo-5-(phenethylamino)-pentanoate (6a)



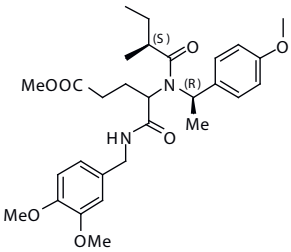
Obtained using procedure A, on 4 mmol scale, starting from *S*-(-)-1-(4-methoxy-phenyl)ethylamine; yield 55% (2.21 mmol, 1106 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.80 (d, *J* = 7.8 Hz, 2H), 7.46 – 7.43 (m, 6H), 7.39 – 7.32 (m, 6H), 7.25 – 7.12 (m, 8H), 7.01 (d, *J* = 7.3 Hz, 4H), 6.76 (d, *J* = 8.6 Hz, 4H), 4.99 (ABq, *J* = 6.8 Hz, 2H), 4.61 (td, *J* = 7.7, 5.2 Hz, 1H), 3.75 (s, 6H), 3.68 (s, 6H), 3.59 – 3.46 (m, 2H), 3.32 (td, *J* = 12.9, 6.7 Hz, 2H), 3.14 (td, *J* = 13.1, 6.9 Hz, 2H), 2.81 (t, *J* = 7.1 Hz, 2H), 2.74 – 2.67 (m, 1H), 2.63 (t, *J* = 7.0 Hz, 2H), 2.62 – 2.43 (m, 4H), 2.28 – 2.21 (m, 2H), 1.61 (d, *J* = 6.9 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 174.4, 173.6, 172.6, 170.9, 167.3, 159.3, 139.1, 138.5, 136.8, 133.4, 131.8, 129.9, 128.8, 128.7, 128.5, 127.1, 126.5, 126.3, 126.2, 114.0, 59.1, 57.6, 55.2, 53.0, 51.9, 51.6, 40.7, 40.2, 35.6, 35.2, 31.0, 30.3, 27.6, 25.4, 17.0. MS (ESI): *m/z* calcd for $C_{30}H_{34}N_2O_5$ $[M]^+$: 502.25; found $[M+H]^+$: 503.35; found $[M+Na]^+$: 525.32, HRMS (ESI): *m/z* calcd for $C_{30}H_{35}O_5N_2$ $[M+H]^+$: 503.25405; found 503.25400.

methyl-4-(N-((*R*)-1-(4-methoxyphenyl)ethyl)acetamido)-5-oxo-5-(phenethylamino) pentanoate (7a)



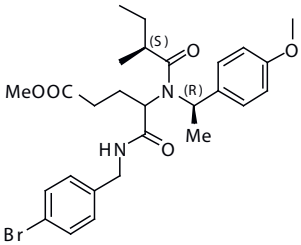
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 53% (0.795 mmol, 350 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.32 (dd, *J* = 13.9, 6.5 Hz, 4H), 7.25 – 7.22 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 3H), 7.16 (d, *J* = 7.3 Hz, 3H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.33 (b, 1H), 4.98 – 4.95 (m, 2H), 3.77 (s, 6H), 3.65 (s, 6H), 3.47 – 3.40 (m, 3H), 3.07 – 3.04 (m, 2H), 2.83 – 2.79 (m, 2H), 2.69 – 2.60 (m, 6H), 2.49 – 2.40 (m, 5H), 2.21 (s, 6H), 1.63 (d, *J* = 7.0 Hz, 3H), 1.43 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 173.8, 172.9, 172.3, 172.0, 170.8, 170.5, 159.3, 159.2, 139.2, 138.9, 131.0, 129.1, 128.9, 128.8, 128.6, 128.6, 128.4, 128.3, 126.6, 126.3, 114.5, 114.1, 114.0, 60.6, 57.7, 56.8, 56.4, 55.3, 55.2, 51.5, 51.4, 40.4, 40.2, 35.4, 35.3, 31.1, 30.9, 25.5, 25.3, 23.8, 23.4, 17.5. MS (ESI): *m/z* calcd for $C_{25}H_{32}N_2O_5$ $[M]^+$: 440.23; found $[M+H]^+$: 441.34; found $[M+Na]^+$: 463.32, HRMS (ESI): *m/z* calcd for $C_{25}H_{33}O_5N_2$ $[M+H]^+$: 441.2384; found 441.23859.

methyl-5-((3,4-dimethoxybenzyl)amino)-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamido)-5-oxopentanoate (8a)



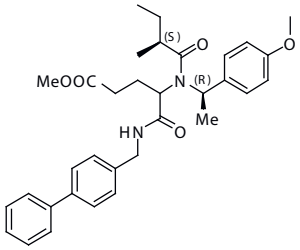
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 52% (0.78 mmol, 412 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.23 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 6.75 (b, 1H), 6.72 – 6.69 (m, 2H), 6.69 (b, 1H), 6.65 – 6.62 (m, 4H), 6.58 (d, *J* = 8.6 Hz, 2H), 6.40 – 6.37 (m, 1H), 5.13-5.10 (m, 2H), 4.33 (dd, *J* = 14.6, 6.3 Hz, 1H), 4.20 (dd, *J* = 14.6, 5.5 Hz, 1H), 4.10 (dd, *J* = 14.4, 5.3 Hz, 1H), 4.00 (dd, *J* = 14.2, 5.5 Hz, 1H),3.79 (s, 6H), 3.77 (s, 6H), 3.73 (s, 3H), 3.67 (s, 3H), 3.60 (s, 3H), 3.44 (s, 3H), 2.71 – 2.52 (m, 4H), 2.45 – 2.39 (m, 3H), 2.31 – 2.27 (m, 1H), 2.00 – 1.95 (m, 1H), 1.87 – 1.83 (m, 2H), 1.78 – 1.66 (m, 2H), 1.61 (t, *J* = 8.2 Hz, 3H), 1.51 – 1.45 (m, 3H), 1.40 – 1.31 (m, 2H), 1.18 – 1.11 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92 – 0.87 (m, 3H), 0.86 – 0.82 (m, 3H), 0.78 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 178.6, 178.3, 173.5, 173.4, 172.5, 172.3, 170.3, 169.5, 159.0, 158.9, 148.7, 147.9, 131.1, 130.7, 128.1, 119.8, 119.5, 113.9, 113.8, 111.1, 110.9, 110.8, 60.9, 57.6, 55.7, 55.5, 55.0, 54.9, 51.3, 51.2, 42.9, 42.8, 39.1, 38.9, 31.0, 30.8, 27.4, 27.2, 25.5, 25.3, 18.3, 18.0, 17.7, 16.8, 12.1, 11.9. MS (ESI): *m/z* calcd for $C_{29}H_{40}N_2O_7$ $[M]^+$: 528.28; found $[M+H]^+$: 529.41; found $[M+Na]^+$: 551.27; found $[M-H]^+$: 527.14.

methyl-5-((4-bromobenzyl)amino)-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamido)-5-oxopentanoate (9a)



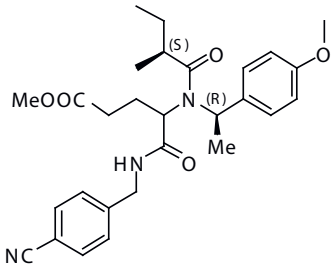
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 50% (0.75 mmol, 410 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.34 – 7.27 (m, 5H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.04 (t, *J* = 8.9 Hz, 4H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.64 – 6.59 (m, 3H), 5.13 – 5.10 (m, 2H), 4.35 (dd, *J* = 15.1, 6.5 Hz, 1H), 4.16 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.06 – 3.97 (m, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 3.57 (s, 3H), 3.42 (s, 3H), 2.75 – 2.66 (m, 3H), 2.58 – 2.49 (m, 1H), 2.42 – 2.34 (m, 5H), 2.16 – 2.10 (m, 1H), 2.00 - 1.96 (m, 1H), 1.85 – 1.79 (m, 2H), 1.76 - 1.63 (m, 3H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.41 – 1.33 (m, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.86 (dd, *J* = 13.8, 6.6 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 178.2, 177.3, 173.4, 172.4, 172.3, 170.4, 169.7, 158.9, 137.5, 137.1, 131.2, 131.1, 130.7, 129.2, 128.8, 128.6, 128.0, 121.1, 120.5, 113.8, 113.7, 60.9, 57.5, 55.0, 54.9, 51.2, 51.1, 42.2, 42.1, 39.0, 38.5, 30.8, 30.6, 27.2, 27.1, 25.3, 25.2, 17.9, 17.7, 17.4, 16.7, 12.1, 11.9. MS (ESI): *m/z* calcd for $C_{27}H_{35}BrN_2O_5$ $[M]^+$:546.17; found $[M+H]^+$: 548.37; found $[M+Na]^+$: 569.29; found $[M+K]^+$: 585.36.

methyl-5-(([1,1′-biphenyl]-4-ylmethyl)amino)-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamido)-5-oxopentanoate (10a)



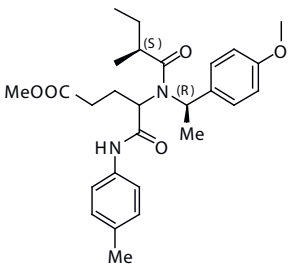
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 37% (0.55 mmol, 302 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.49 – 7.46 (m, 5H), 7.44 – 7.39 (m, 5H), 7.36 – 7.30 (m, 5H), 7.26 – 7.22 (m, 2H), 7.16 – 7.14 (m, 2H), 7.07 (dd, *J* = 13.6, 8.2 Hz, 5H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 2H), 5.12 – 5.09 (m, 2H), 4.46 (dd, *J* = 14.9, 6.4 Hz, 1H), 4.25 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.21 – 4.16 (m, 1H), 3.70 (s, 3H), 3.58 (s, 6H), 3.42 (s, 3H), 2.76 – 2.53 (m, 5H), 2.42 (dd, *J* = 14.0, 7.0 Hz, 3H), 2.36 – 2.33 (m, 2H), 2.13 – 2.10 (m, 1H), 2.02 – 1.98 (m, 1H), 1.89 – 1.82 (m, 2H), 1.76 – 1.63 (m, 3H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.47 (dd, *J* = 19.1, 7.0 Hz, 3H), 1.36 (m, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.86 (td, *J* = 15.6, 7.0 Hz, 6H), 0.77 (t, *J* =7.3 Hz, 3H) .^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 178.4, 177.7, 173.6, 173.5, 172.6, 172.3, 170.5, 169.8, 159.1, 159.0, 140.6, 140.4, 140.3, 139.9, 139.8, 137.6, 137.1, 135.5, 131.3, 130.9, 128.6, 128.5, 128.2, 128.1, 127.7, 127.1, 127.0, 126.9, 126.7, 114.4, 114.0, 113.9, 113.7, 61.2, 57.9, 55.2, 54.9, 51.4, 42.7, 42.6, 39.3, 38.8, 31.6, 31.0, 27.6, 27.3, 25.6, 25.4, 17.9, 17.7, 12.3, 12.1. MS (ESI): *m/z* calcd for $C_{33}H_{40}N_2O_5$ $[M]^+$:544.29; found $[M+H]^+$: 545.22; found $[M+Na]^+$: 567.27; found $[M+K]^+$: 583.40, HRMS (ESI): *m/z* calcd for $C_{33}H_{41}O_5N_2$ $[M+H]^+$: 545.3010; found 545.30115.

methyl-5-((4-cyanobenzyl)amino)-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methyl butanamido)-5-oxopentanoate (11a)



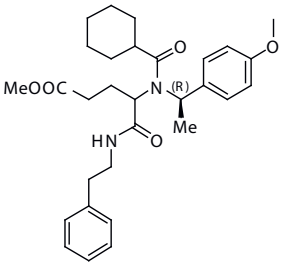
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 40% (0.60 mmol, 300 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.12 (dd, *J* = 8.0, 3.7 Hz, 5H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.21 – 5.14 (m, 2H), 4.48 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.32 (dd, *J* = 15.7, 5.6 Hz, 1H), 4.16 (d, *J* = 5.0 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.62 (s, 3H), 3.46 (s, 3H), 2.82 – 2.80 (m, 1H), 2.75 – 2.68 (m, 2H), 2.48 – 2.37 (m, 4H), 2.01 - 1.98 (m, 1H), 1.89 – 1.68 (m, 5H), 1.63 (d, *J* = 7.0 Hz, 3H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.47 – 1.34 (m, 3H), 1.06 – 1.00 (m, 6H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.88 – 0.76 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 178.4, 177.6, 173.5, 172.7, 172.5, 170.9, 159.1, 144.1, 143.8, 132.1, 132.0, 131.8, 128.2, 127.9, 127.7, 118.6, 118.5, 114.0, 113.9, 110.7, 110.6, 61.0, 57.7, 55.2, 55.1, 55.0, 54.9, 51.4, 42.5, 42.4, 39.1, 38.6, 30.8, 27.3, 27.2, 25.6, 25.4, 18.1, 17.9, 12.2, 12.1. MS (ESI): *m/z* calcd for $C_{28}H_{35}N_3O_5$ $[M]^+$: 493.26; found $[M+H]^+$: 494.31; found $[M+Na]^+$: 516.37; found $[M+K]^+$: 532.24, HRMS (ESI): *m/z* calcd for $C_{28}H_{36}O_5N_3$ $[M+H]^+$: 494.26495; found 494.26508.

methyl-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamido)-5-oxo-5-(p-tolylamino)pentanoate (12a)



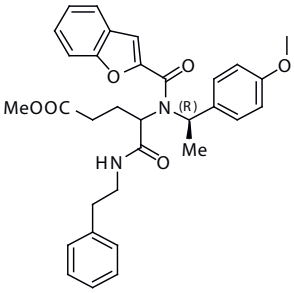
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 36% (0.54 mmol, 253 mg), red oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 10.17 (s, 1H), 8.88 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.21 (dd, *J* =16.1, 7.7 Hz, 3H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.03 – 6.98 (m, 3H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.25-5.19 (m, 2H), 4.27 (t, *J* = 7.1 Hz, 1H), 4.08 (dt, *J* = 14.3, 6.8 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.49 (s, 3H), 2.74 – 2.71 (m, 1H), 2.47 – 2.34 (m, 3H), 2.27 (s, 3H), 2.23 (s, 3H), 2.14 – 2.03 (m, 2H), 1.96 – 1.84 (m, 4H), 1.70 (d, *J* = 7.0 Hz, 3H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.53 – 1.41 (m, 4H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.95 – 0.88 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 179.9, 179.1, 173.3, 172.5, 170.4, 168.8, 159.6, 159.1, 135.6, 135.4, 134.3, 133.7, 133.3, 133.0, 129.1, 129.0, 128.2, 128.1, 119.7, 119.5, 114.1, 113.9, 62.4, 59.7, 55.2, 55.0, 51.9, 51.4, 40.6, 39.4, 30.7, 28.8, 27.5, 27.3, 25.2, 23.7, 21.9, 20.7, 20.6, 18.0, 17.6, 12.2, 12.0. MS (ESI): *m/z* calcd for $C_{27}H_{36}N_2O_5$ $[M]^+$:468.26; found $[M+H]^+$: 469.24; found $[M+Na]^+$: 491.35; found $[M+K]^+$: 507.23, HRMS (ESI): *m/z* calcd for $C_{27}H_{37}O_5N_2$ $[M+H]^+$: 469.2697; found 469.26959.

methyl-4-(N-((*R*)-1-(4-methoxyphenyl)ethyl)cyclohexanecarboxamido)-5-oxo-5-(phenethylamino)-pentanoate (13a)



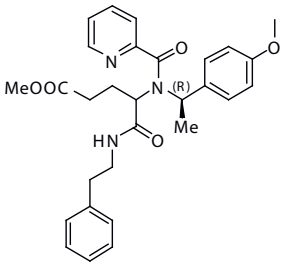
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 55% (0.825 mmol, 420 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.38 (d, *J* = 8.7 Hz, 1H), 7.30 – 7.27 (m, 3H), 7.22 – 7.17 (m, 5H), 7.16 (d, *J* = 7.4 Hz, 3H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 3H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.10 – 5.03 (ABq, *J* = 6.4 Hz, 2H), 4.34 (t, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.62 – 3.54 (m, 2H), 3.46 (s, 3H), 3.38 – 3.30 (m, 2H), 2.81 – 2.77 (m, 1H), 2.71 – 2.62 (m, 2H), 2.60 – 2.55 (m, 2H), 2.52 – 2.45 (m, 3H), 2.36 (m, 3H), 2.26 (dd, *J* = 15.4, 7.4 Hz, 2H), 2.00 – 1.91 (m, 3H), 1.82 – 1.81 (m, 2H), 1.77 – 1.74 (m, 4H), 1.65 (d, *J* = 7.0 Hz, 6H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.23 (dt, *J* = 13.7, 5.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 177.8, 177.4, 173.2, 172.5, 170.7, 158.8, 158.7, 138.8, 138.6, 131.3, 131.1, 128.9, 128.4, 128.1, 128.0, 126.1, 126.0, 113.7, 113.6, 60.1, 58.1, 54.9, 54.9, 51.2, 50.7, 42.7, 42.4, 40.4, 40.1, 35.2, 35.1, 30.7, 30.0, 29.0, 27.4, 25.3, 25.2, 21.8, 18.0, 17.9. MS (ESI): *m/z* calcd for $C_{30}H_{40}N_2O_5$ $[M]^+$:508.29; found $[M+H]^+$: 509.43; found $[M+Na]^+$: 531.36; found $[M+K]^+$: 547.43.

methyl-4-(N-((*R*)-1-(4-methoxyphenyl)ethyl)benzofuran-2-carboxamido)-5-oxo-5-(phenethylamino)pentanoate (14a)



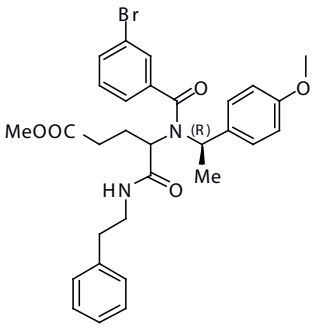
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 24% (0.36 mmol, 195 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 7.75 (d, *J* = 7.7 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.60 – 7.59 (m, 3H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.49 – 7.48 (m, 2H), 7.45 – 7.44 (m, 2H), 7.37 – 7.35 (m, 2H), 7.26 (d, *J* = 6.7 Hz, 4H), 7.24 – 1.18 (m, 4H), 7.08 – 7.07 (m, 3H), 6.73 (d, *J* = 8.3 Hz, 4H), 5.66 (b, 2H), 4.73 – 4.70 (m, 2H), 3.77 (s, 6H), 3.67 (s, 6H), 3.64 – 3.58 (m, 2H), 3.46 – 3.42 (m, 2H), 2.86 (t, *J* = 7.1 Hz, 2H), 2.69 – 2.60 (m, 4H), 2.57 – 2.50 (m, 4H), 2.42 – 2.39 (m, 2H), 1.84 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 173.8, 173.6, 170.5, 170.3, 161.4, 159.4, 158.8, 154.8, 154.7, 149.1, 148.0, 139.2, 138.5, 128.9, 128.8, 128.6, 128.4, 127.4, 126.9, 126.5, 126.3, 123.9, 123.7, 122.8, 122.5, 122.3, 114.1, 113.9, 112.8, 112.7, 112.1, 111.8, 110.9, 110.8, 59.2, 56.9, 55.3, 55.1, 52.2, 40.8, 40.5, 35.5, 35.3, 31.1, 30.2, 28.1, 25.0. MS (ESI): *m/z* calcd for $C_{32}H_{34}N_2O_6$ $[M]^+$: 542.24; found $[M+H]^+$: 543.27; found $[M+Na]^+$: 565.32; found $[M+K]^+$: 581.26.

methyl-4-(N-((*R*)-1-(4-methoxyphenyl)ethyl)picolinamido)-5-oxo-5-(phenethylamino)-pentanoate (15a)



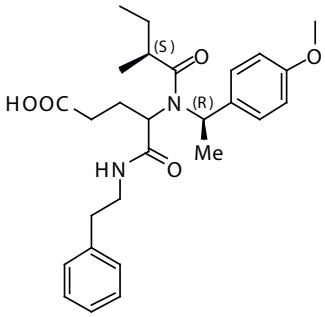
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 41% (0.61 mmol, 309 mg), yellow oil.[1]H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 8.90 (b, 1H), 8.68 (b, 1H), 8.61 – 8.55 (m, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.91 – 7.75 (m, 4H), 7.72 – 7.71(m, 1H), 7.50 – 7.48 (m, 5H), 7.24 – 7.14 (m, 9H), 6.93 – 6.73 (m, 5H), 5.28 – 5.27 (m, 1H), 4.69 – 4.59 (m, 3H), 3.77 (s, 6H), 3.73 – 3.69 (m, 2H), 3.66 (s, 3H), 3.56 – 3.53 (m, 2H), 3.46 (s, 3H), 2.86 – 2.82 (m, 2H), 2.77 – 2.75 (m, 1H), 2.67 – 2.64 (m, 2H), 2.56 – 2.50 (m, 1H), 2.44 – 2.36 (m, 1H), 2.30 (b, 3H), 2.09 (dd, *J* = 14.3, 7.0 Hz, 2H), 1.94 – 1.89 (m, 6H).[13]C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 173.5, 172.5, 170.2, 169.5, 169.2, 167.9, 159.1, 158.3, 154.3, 153.8, 148.3, 146.6, 146.4, 138.7, 137.7, 137.1, 136.9, 128.5, 128.3, 126.1, 124.5, 113.6, 112.8, 59.9, 56.8, 54.9, 51.2, 40.2, 40.0, 35.2, 35.0, 30.9, 29.8, 25.2, 23.9, 18.5, 16.9. MS(ESI): *m/z* calcd for $C_{29}H_{33}N_3O_5$ $[M]^+$: 503.24; found $[M+Na]^+$: 526.26; found $[M+K]^+$: 542.26, HRMS (ESI): *m/z* calcd for $C_{29}H_{34}O_5N_3$ $[M+H]^+$: 504.2493; found 504.24948.

methyl-4-(3-bromo-N-((*R*)-1-(4-methoxyphenyl)ethyl)benzamido)-5-oxo-5-(phenethyl amino)–pentanoate (16a)



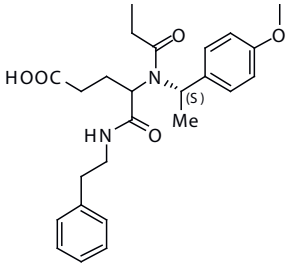
Obtained using procedure A, on 1.5 mmol scale, starting from *R*-(+)-1-(4-methoxy-phenyl)ethylamine; yield 29% (0.435 mmol, 253 mg), yellow oil. [1]H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 8.01 – 8.00 (m, 2H), 7.76 (dd, *J* = 14.3, 8.2 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.58 (dd, *J* = 14.0, 6.8 Hz, 2H), 7.39 – 7.33 (m, 4H), 7.33 – 7.27 (m, 6H), 7.22 – 7.20 (m, 6H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.85 – 6.83 (m, 2H), 4.98 – 4.96 (m, 1H), 4.66 (dd, *J* = 13.0, 7.5 Hz, 3H), 3.85 (s, 3H), 3.69 (s, 6H), 3.65 – 3.61 (m, 2H), 3.59 (s, 3H), 3.55 – 3.51 (m, 2H), 2.95 – 2.90 (m, 2H), 2.85 (t, *J* = 7.1 Hz, 4H), 2.61 – 2.51 (m, 2H), 2.43 – 2.38 (m, 2H), 2.22 – 2.15 (m, 2H), 2.14 – 2.05 (m, 3H), 1.45 (d, *J* = 6.4 Hz, 3H). [13]C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers) δ 174.2, 174.1, 171.3, 170.9, 165.9, 159.4, 138.7, 138.5, 135.4, 134.8, 134.6, 132.8, 132.6, 130.6, 130.4, 130.0, 128.7, 128.5, 126.5, 125.7, 125.5, 124.3, 123.0, 122.7, 114.1, 114.0, 61.0, 58.2, 53.0, 51.9, 51.4, 40.7, 40.2, 35.5, 35.2, 30.2, 27.5, 25.5. MS (ESI): *m/z* calcd for $C_{30}H_{33}BrN_2O_5$ $[M]^+$:580.16; found $[M+Na]^+$: 603.19; found $[M+K]^+$: 619.25.

4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamido)-5-oxo-5-(phenethylamino)-pentanoic acid (3b)



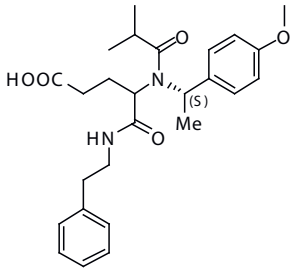
Obtained using procedure B; yield 95% (2.28 mmol, 1070 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.37 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.25 (m, 6H), 7.23 – 7.21 (m, 4H), 7.16 (d, *J* = 7.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 7.1 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 5.19 – 5.13 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.63 – 3.57 (m, 1H), 3.47 – 3.42 (m, 1H), 3.33 (d, *J* = 5.3 Hz, 3H), 2.81 (dd, *J* = 10.8, 6.7 Hz, 1H), 2.69 – 2.62 (m, 6H), 2.46 – 2.43 (m, 1H), 2.39 (d, *J* = 6.6 Hz, 3H), 2.01 – 1.94 (m, 3H), 1.82 – 1.77 (m, 1H), 1.73 – 1.70 (m, 1H), 1.67 (d, *J* = 6.8 Hz, 3H), 1.55- 1.53 (m, 1H), 1.50 (d, *J* = 6.9 Hz, 3H), 1.48 – 1.43 (m, 2H), 0.96 (dt, *J* = 15.3, 6.8 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 178.9, 178.7, 177.1, 176.2, 173.2, 171.7, 159.2, 159.1, 138.8, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 126.5, 126.4, 114.1, 114.0, 60.6, 58.6, 55.3, 40.6, 40.4, 39.5, 39.3, 35.4, 30.9, 30.8, 27.6, 27.4, 25.3, 25.2, 18.1, 17.8, 17.3, 17.0, 12.4, 12.2. MS (ESI): *m/z* calcd for $C_{27}H_{36}N_2O_5$ $[M]^+$: 468.26 ; found $[M+H]^+$: 469.30; found $[M+Na]^+$: 491.23**.** HRMS (ESI): *m/z* calcd for $C_{27}H_{37}O_5N_2$ $[M+H]^+$: 469.26970; found 469.26971.

4-(N-((*S*)-1-(4-methoxyphenyl)ethyl)propionamido)-5-oxo-5-(phenethylamino)pentanoic acid (4b)



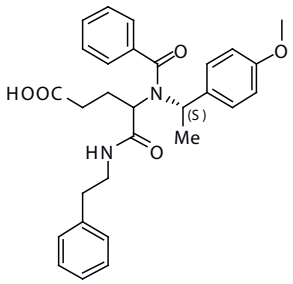
Obtained using procedure B; yield 99% (2.06 mmol, 907 mg), brown oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.37 – 7.31 (m, 4H), 7.31 – 7.26 (m, 3H), 7.22 (d, *J* = 8.2 Hz, 4H), 7.17 (d, *J* = 7.3 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.81 (s, 1H), 6.74 (d, *J* = 8.3 Hz, 2H), 5.06 (ABq, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.63 – 3.57 (m, 2H), 3.49 – 3.40 (m, 2H), 3.13 – 3.11 (m, 1H), 2.87 – 2.80 (m, 2H), 2.72 – 2.58 (m, 5H), 2.50 – 2.38 (m, 6H), 2.02 – 1.90 (m, 4H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.18 (dt, *J* = 14.4, 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 176.8, 176.5, 175.4, 174.6, 172.8, 171.4, 159.2, 159.1, 139.1, 138.8, 130.9, 128.8, 128.7, 128.4, 128.2, 127.3, 126.4, 126.3, 114.1, 60.2, 58.1, 55.2, 40.4, 35.3, 35.2, 31.0, 30.7, 28.4, 28.1, 25.4, 25.0, 21.5, 20.78, 17.7, 17.5, 9.5, 9.4. MS (ESI): *m/z* calcd for $C_{25}H_{32}N_2O_5$ $[M]^+$: 440.23; found $[M+H]^+$: 441.33; found $[M+Na]^+$: 463.32; found $[M+K]^+$: 479.19; found $[M-H]^+$: 439.25, HRMS (ESI): *m/z* calcd for $C_{25}H_{33}O_5N_2$ $[M+H]^+$: 441.23840; found 441.23834.

4-(N-((*S*)-1-(4-methoxyphenyl)ethyl)isobutyramido)-5-oxo-5-(phenethylamino)pentanoic acid (5b)



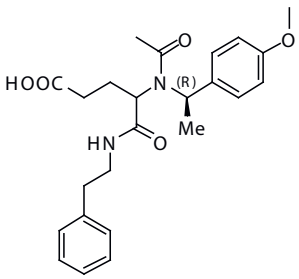
Obtained using procedure B; yield 95% (1.97 mmol, 900 mg), light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.33 – 7.29 (m, 6H), 7.25 – 7.17 (m, 8H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.14 (dd, *J* = 13.0, 6.8 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.61 – 3.59 (m, 1H), 3.50 – 3.48 (m, 1H), 3.38 – 3.32 (m, 2H), 2.85 – 2.80 (m, 3H), 2.75 – 2.68 (m, 3H), 2.59 – 2.55 (m, 2H), 2.39 (t, *J* = 6.7 Hz, 4H), 2.06 – 2.04 (m, 2H), 1.98 – 1.95 (m, 2H), 1.68 (d, *J* = 7.0 Hz, 3H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 6H), 1.00 (d, *J* = 5.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 179.4, 179.2, 177.1, 176.3, 172.6, 171.5, 159.1, 159.0, 138.9, 138.7, 131.4, 129.1, 128.6, 128.4, 128.3, 128.0, 126.4, 126.3, 114.0, 113.9, 59.9, 58.5, 55.2, 54.9, 54.4, 40.5, 40.4, 35.4, 35.2, 32.3, 32.2, 30.9, 30.7, 25.2, 25.0, 20.4, 20.2, 19.7, 19.6, 19.4, 19.3, 18,4, 18.3. MS (ESI): *m/z* calcd for $C_{26}H_{34}N_2O_5$ $[M]^+$: 454.25; found $[M+H]^+$: 455.31; found $[M+Na]^+$: 477.18; found $[M+K]^+$: 493.24; found $[M-H]^+$: 453.17, HRMS (ESI): *m/z* calcd for $C_{26}H_{35}O_5N_2$ $[M+H]^+$: 455.25405; found 455.25427.

4-(N-((*S*)-1-(4-methoxyphenyl)ethyl)benzamido)-5-oxo-5-(phenethyl amino)pentanoic acid (6b)



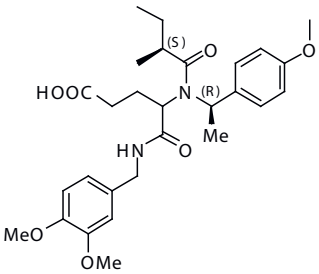
Obtained using procedure B; yield 85% (1.88 mmol, 918 mg), white Ugi foam.^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.90 (dd, *J* = 7.1, 4.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.50 – 7.46 (m, 4H), 7.44 – 7.42 (m, 4H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.22 (m, 4H), 7.20 – 7.14 (m, 6H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.23 (q, *J* = 6.8 Hz, 1H), 5.02 (q, *J* = 7.0 Hz, 1H), 3.99 (dd, *J* = 15.7, 8.2 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.58 – 3.48 (m, 3H), 3.33 – 3.28 (m, 1H), 3.17 – 3.12 (m, 1H), 2.85 – 2.78 (m, 5H), 2.66 (t, *J* = 7.0 Hz, 3H), 2.47 (t, *J* = 6.8 Hz, 3H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.59 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 175.8, 173.1, 172.2, 171.8, 170.9, 159.3, 159.2, 138.8, 138.5, 136.4, 135.9, 133.0, 131.9, 130.1, 129.5, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 126.3, 126.0, 125.9, 113.8, 113.7, 59.0, 58.0, 56.5, 55.1, 54.4, 52.7, 41.4, 40.3, 35.3, 34.9, 31.6, 30.6, 25.0, 22.8, 19.4, 16.6. MS (ESI): *m/z* calcd for $C_{29}H_{32}N_2O_5$ $[M]^+$: 488.58; found $[M-H]^+$: 487.45, HRMS (ESI): *m/z* calcd for $C_{29}H_{33}O_5N_2$ $[M+H]^+$: 489.2384; found 489.23843.

4-(N-((*R*)-1-(4-methoxyphenyl)ethyl)acetamido)-5-oxo-5-(phenethylamino)pentanoic acid (7b)



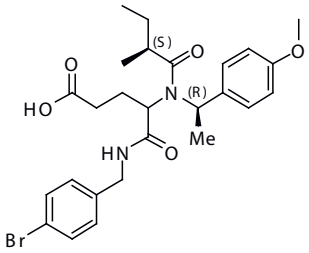
Obtained using procedure B; yield 98% (0.78 mmol, 332 mg), yellow oil.[1]H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.34 – 7.29 (m, 5H), 7.25 – 7.16 (m, 8H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 3H), 4.99 (dd, *J* = 12.8, 6.3 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.57 – 3.52 (m, 1H), 3.49 – 3.44 (m, 1H), 3.43 – 3.38 (m, 1H), 3.12 – 3.08 (m, 1H), 2.85 – 2.78 (m, 2H), 2.70 – 2.59 (m, 4H), 2.46 – 2.43 (m, 3H), 2.39 – 2.32 (m, 1H), 2.21 (s,6H), 2.00 – 1.85 (m, 4H), 1.62 (d, *J* = 7.0 Hz, 3H), 1.42 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 176.4, 176.2, 172.3, 171.4, 171.2, 159.3, 159.2, 139.1, 138.8, 130.8, 128.9, 128.8, 128.5, 128.4, 128.3, 126.4, 114.5, 114.2, 60.0, 58.0, 55.3, 40.5, 40.4, 35.4, 35.2, 31.0, 30.7, 25.4, 25.0, 23.8, 23.5, 17.6, 17.5. MS (ESI): *m/z* calcd for $C_{24}H_{30}N_2O_5$ $[M]^+$: 426.22; found $[M+H]^+$: 427.21; found $[M+Na]^+$: 449.26; found $[M+K]^+$: 465.39; found $[M-H]^+$: 425.26, HRMS (ESI): *m/z* calcd for $C_{24}H_{31}O_5N_2$ $[M+H]^+$: 427.22275; found 427.22266.

5-((3,4-dimethoxybenzyl)amino)-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methyl butanamido) -5-oxopentanoic acid (8b)



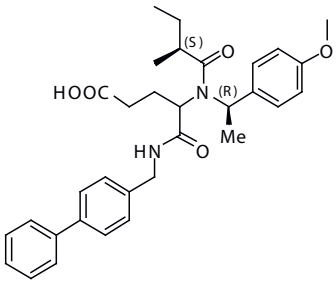
Obtained using procedure B; yield 80% (0.62 mmol, 321 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.23 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 1H), 6.78 (b, 1H), 6.77 – 6.69 (m, 3H), 6.68 (b, 1H), 6.63 (d, *J* = 8.6 Hz, 4H), 6.58 (d, *J* = 8.3 Hz, 1H), 6.42 – 6.40 (m, 1H), 5.18 – 5.13 (m, 2H), 4.37 (dd, *J* = 14.6, 6.2 Hz, 1H), 4.23 (dd, *J* = 14.6, 5.5 Hz, 1H), 4.15 – 4.13 (m, 1H), 4.07 – 4.04 (m, 1H), 3.81 (s, 6H), 3.79 (s, 6H), 3.72 (s, 3H), 3.68 (s, 3H), 2.72 – 2.63 (m, 4H), 2.44 (t, *J* = 7.0 Hz, 3H), 2.33 – 2.30 (m, 1H), 1.96 – 1.89 (m, 3H), 1.65 (d, *J* = 7.7 Hz, 3H), 1.52 (d, *J* = 7.2 Hz, 3H), 1.41 – 1.34 (m, 3H), 1.21 – 1.10 (m, 2H), 0.98 – 0.87 (m, 9H), 0.81 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 178.7, 178.5, 176.7, 176.5, 172.6, 170.9, 159.1, 158.9, 148.9, 148.7, 148.3, 148.0, 130.9, 130.5, 129.0, 128.8, 128.0, 120.0, 119.7, 113.9, 111.2, 110.9, 60.5, 57.8, 55.7, 55.6, 55.0, 43.0, 39.3, 39.0, 30.8, 30.6, 27.4, 27.2, 25.2, 25.0, 18.1, 17.6, 16.8, 16.2, 12.1, 11.9. MS (ESI): *m/z* calcd for $C_{28}H_{38}N_2O_7$ $[M]^+$: 514.27; found $[M+H]^+$: 515.42; found $[M+Na]^+$: 537.35; found $[M+K]^+$: 553.35; found $[M-H]^+$: 513.28.

5-((4-bromobenzyl)amino)-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methyl-butanamido)-5-oxopentanoic acid (9b)



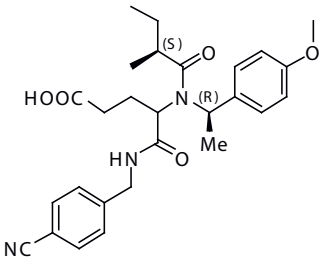
Obtained using procedure B; yield 78% (0.585 mmol, 312 mg), colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.41 – 7.36 (m, 5H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.2 Hz, 3H), 5.22 – 5.18 (m, 2H), 4.45 (dd, *J* = 15.0, 6.4 Hz, 1H), 4.25 (dd, *J* = 15.2, 5.4 Hz, 1H), 4.15 (dt, *J* = 14.3, 11.2 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 2.70 – 2.67 (m, 4H), 2.47 (t, *J* = 6.6 Hz, 3H), 2.04 – 1.92 (m, 4H), 1.91 – 1.85 (m, 1H), 1.80 – 1.78 (m, 2H), 1.67 (d, *J* = 6.9 Hz, 3H), 1.55 (d, *J* = 6.9 Hz, 3H), 1.48 – 1.42 (m, 4H), 1.26 – 1.23 (m, 1H), 1.19 – 1.16 (m, 1H), 1.03 (d, *J* = 5.5 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 179.0, 178.6, 177.0, 176.8, 172.8, 171.2, 159.2, 159.1, 137.5, 137.2, 131.5, 131.4, 129.5, 129.2, 128.9, 128.3, 121.0, 114.1, 114.0, 60.8, 58.1, 55.8, 55.3, 55.1, 54.7, 43.0, 42.6, 39.8, 39.1, 30.9, 30.6, 27.7, 27.4, 25.4, 25.1, 18.2, 17.8, 17.6, 16.9, 12.4, 12.1. MS (ESI): *m/z* calcd for $C_{26}H_{33}BrN_2O_5$ $[M]^+$: 532.16; found $[M+H]^+$: 533.25; found $[M+Na]^+$: 555.23; found $[M-H]^+$: 531.11.

5-(([1,1′-biphenyl]-4-ylmethyl)amino)-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methyl butanamido)-5-oxopentanoic acid (10b)



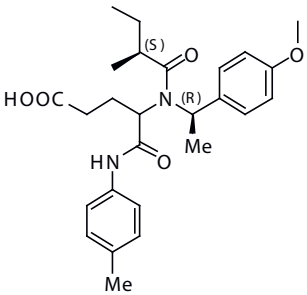
Obtained using procedure B; yield 90% (0.495 mmol, 263 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.61 – 7.58 (m, 5H), 7.54 – 7.51 (m, 5H), 7.46 – 7.40 (m, 5H), 7.37 – 7.33 (m, 5H), 7.23 – 7.21 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.67 (dd, *J* = 12.7, 8.6 Hz, 2H), 5.22 (dd, *J* = 11.2, 6.9 Hz, 2H), 4.58 (dd, *J* = 14.9, 6.4 Hz, 1H), 4.37 (dd, *J* = 14.9, 5.0 Hz, 1H), 4.28 – 4.25 (m, 2H), 3.77 (s, 3H), 3.67 (s, 3H), 2.74 – 2.71 (m, 4H), 2.51 (t, *J* = 6.6 Hz, 3H), 2.10 – 2.02 (m, 3H), 1.76 – 1.71 (m, 1H), 1.69 (d, *J* = 6.9 Hz, 3H), 1.59 (d, *J* = 6.9 Hz, 3H), 1.55 – 1.53 (m, 1H), 1.51 – 1.45 (m, 3H), 1.22 – 1.14 (m, 1H) 1.04 – 0.91 (m, 9H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 178.9, 178.6, 176.7, 176.6, 171.2, 170.0, 159.2, 159.0, 140.7, 140.0, 137.4, 137.0, 128.7, 128.3, 127.8, 127.2, 127.1, 126.9, 114.5, 114.0, 60.7, 58.2, 55.2, 55.1, 43.5, 42.9, 39.5, 39.2, 30.9, 30.6, 30.2, 29.6, 27.5, 27.3, 25.3, 25.1, 18.3, 17.8, 12.3, 12.1. MS (ESI): *m/z* calcd for $C_{32}H_{38}N_2O_5$ $[M]^+$: 530.28; found $[M+H]^+$: 531.42; found $[M+Na]^+$: 553.35; $[M+K]^+$: 569.35; found $[M-H]^+$: 529.28, HRMS (ESI): *m/z* calcd for $C_{32}H_{39}O_5N_2$ $[M+H]^+$: 531.28535; found 531.28546.

5-((4-cyanobenzyl)amino)-4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamido)-5-oxopentanoic acid (11b)



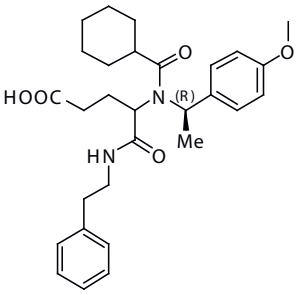
Obtained using procedure B; yield 86% (0.516 mmol, 247 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.55 (dd, *J* = 14.9, 8.1 Hz, 5H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 5H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 5.23 – 5.20 (m, 2H), 4.53 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.37 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.26 – 4.24 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 2.82 – 2.67 (m, 3H), 2.46 – 2.44 (m, 3H), 2.02 – 1.94 (m, 4H), 1.84 – 1.73 (m, 4H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.48 – 1.45 (m, 2H), 1.04 (d, *J* = 5.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 6H), 0.86 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 179.0, 177.0, 176.8, 172.9, 171.5, 159.3, 159.2, 144.1, 143.7, 132.2, 132.1, 128.3, 128.1, 128.0, 118.7, 114.1, 110.9, 110.8, 60.7, 58.2, 55.2, 42.8, 42.7, 39.4, 39.0, 30.8, 30.5, 30.2, 29.6, 27.4, 27.3, 25.3, 25.0, 18.3, 17.8, 12.3, 12.1. MS (ESI): *m/z* calcd for $C_{27}H_{33}N_3O_5$ $[M]^+$: 479.24; found $[M+H]^+$: 480.20; found $[M+Na]^+$: 502.25; $[M+K]^+$: 518.26; found $[M-H]^+$: 478.31, HRMS (ESI): *m/z* calcd for $C_{27}H_{34}O_5N_3$ $[M+H]^+$: 480.2493; found 480.24933.

4-((*S*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamido)-5-oxo-5-(p-tolylamino) pentanoic acid (12b)



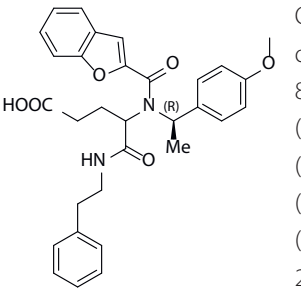
Obtained using procedure B; yield 96% (0.52 mmol, 235 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 10.16 (b, 1H), 9.19 (b, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.28 (m, 1H), 7.23 – 7.16 (m, 3H), 7.10 (d, *J* = 8.2 Hz, 2H),7.05 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 5.26 (dd, *J* = 15.8, 7.1 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 2.73 – 2.70 (m, 2H), 2.58 – 2.54 (m, 2H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 2.16 – 2.07 (m, 2H), 1.71 (d, *J* = 6.7 Hz, 3H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.53 – 1.48 (m, 2H), 1.26 (b, 3H), 1.07 (b, 3H), 1.02 – 0.89 (m, 9H), 0.89 (dd, *J* = 13.2, 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 179.5, 179.2, 177.2, 177.1, 170.6, 169.4, 159.7, 159.2, 135.6, 135.3, 133.7, 133.4, 129.3, 129.2, 128.2, 119.9, 119.7, 114.2, 114.1, 61.7, 59.9, 55.3, 55.2, 39.7, 39.4, 30.6, 30.5, 29.6, 28.7, 27.6, 27.4, 25.0, 24.9, 20.8, 18.3, 17.9, 17.1, 16.3, 12.3, 12.1. MS (ESI): *m/z* calcd for $C_{26}H_{34}N_2O_5$ $[M]^+$: 454.25; found $[M+H]^+$: 455.25; found $[M+Na]^+$: 477.30; found $[M-H]^+$: 453.23, HRMS (ESI): *m/z* calcd for $C_{26}H_{35}O_5N_2$ $[M+H]^+$: 455.25405; found 455.25403.

4-(N-((*R*)-1-(4-methoxyphenyl)ethyl)cyclohexanecarboxamido)-5-oxo-5-(phenethylamino)-pentanoic acid (13b)



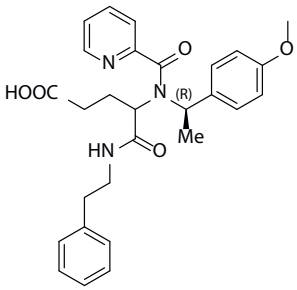
Obtained using procedure B; yield 82% (0.67 mmol, 334 mg), colourless oil.^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.37 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.29 (m, 6H), 7.25 – 7.19 (m, 7H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.92 – 6.90 (m, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.13 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.65 – 3.53 (m, 1H), 3.50 – 3.46 (m, 1H), 3.40 – 3.30 (m, 2H), 2.86 – 2.81 (m, 1H), 2.76 – 2.67 (m, 3H), 2.64 – 2.54 (m, 3H), 2.49 (t, *J* = 7.1 Hz, 3H), 2.38 (t, *J* = 6.6 Hz, 4H), 2.07 – 2.00 (m, 2H), 1.96 – 1.88 (m, 4H), 1.85 – 1.83 (m, 2H), 1.79 – 1.76 (m, 4H), 1.68 (d, *J* = 6.9 Hz, 6H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.33 – 1.23 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 178.4, 178.3, 177.5, 176.6, 172.8, 171.6, 159.1, 159.0, 138.9, 138.7, 131.5, 128.7, 128.4, 128.1, 126.3, 114.0, 113.9, 61.8, 58.5, 55.8, 55.3, 42.9, 42.8, 40.8, 40.5, 35.3, 35.2, 30.8, 29.6, 27.8, 27.3, 25.8, 25.7, 25.5, 25.3, 18.4, 18.2. MS (ESI): *m/z* calcd for $C_{29}H_{38}N_2O_5$ $[M]^+$: 494.28; found $[M+H]^+$:495.32; found $[M+Na]^+$: 517.37.

4-(N-((*R*)-1-(4-methoxyphenyl)ethyl)benzofuran-2-carboxamido)-5-oxo-5-(phenethylamino) -pentanoic acid (14b)



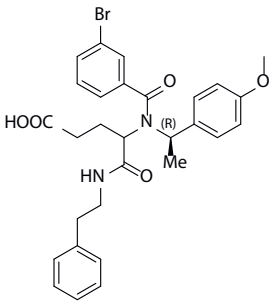
Obtained using procedure B; yield 97% (0.35 mmol, 185 mg), yellow oil.^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.50 – 7.43 (m, 5H), 7.40 – 7.33 (m, 4H), 7.25 – 7.23 (m, 4H), 7.19 – 7.16 (m, 4H), 7.01 (d, *J* = 5.8 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 4H), 5.57 (b, 2H), 4.82 – 4.74 (m, 2H), 3.72 (s, 6H), 3.56 – 3.43 (m, 4H), 3.38 – 3.34 (m, 1H), 2.84 – 2.81 (m, 1H), 2.79 – 2.76 (m, 2H), 2.67 – 2.59 (m, 5H), 2.52 – 2.48 (m, 2H), 2.23 – 2.16 (m, 1H), 1.84 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 176.4, 176.2, 171.5, 171.0, 162.4, 161.9, 159.3, 159.1, 154.9, 154.7, 148.8, 147.6, 139.0, 138.5, 129.0, 128.8, 128.7, 128.4, 127.3, 126.8, 126.3, 123.8, 123.7, 122.5, 122.3, 114.0, 113.8, 113.0, 112.9, 112.0, 111.8, 59.4, 57.4, 55.2, 55.1, 40.9, 40.6, 35.4, 35.1, 30.7, 27.8, 24.7. MS (ESI): *m/z* calcd for $C_{31}H_{32}N_2O_6$ $[M]^+$: 528.23; found $[M+Na]^+$: 551.21; found $[M-H]^+$: 527.08, HRMS (ESI): *m/z* calcd for $C_{31}H_{33}O_6N_2$ $[M+H]^+$:529.23331; found 529.23334.

4-(N-((*R*)-1-(4-methoxyphenyl)ethyl)picolinamido)-5-oxo-5-(phenethylamino)pentanoic acid (15b)



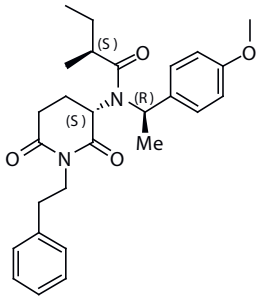
Obtained using procedure B; yield 71% (0.43 mmol, 212 mg), brown oil.[1]H NMR (500 MHz, MeOD, mixture of diastereomers) δ 8.68 – 8.66 (m, 1H), 7.96 – 7.88 (m, 2H), 7.61 (d, *J* = 6.8 Hz, 2H), 7.51 – 7.50 (m, 1H), 7.42 – 7.40 (m, 1H), 7.35 – 7.33 (m, 1H), 7.27 – 7.18 (m, 10H), 7.13 (d, *J* = 7.0 Hz, 4H), 6.90 – 6.88 (m, 1H), 6.81 – 6.80 (m, 3H), 5.05 – 5.03 (m, 2H), 4.74 – 4.72 (m, 1H), 4.60 – 4.58 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.60 – 3.48 (m, 2H), 3.38 – 3.25 (m, 2H), 3.06 – 3.05 (m, 1H), 2.86 – 2.83 (m, 1H), 2.73 – 2.70 (m, 2H), 2.57 – 2.52 (m, 4H), 2.39 – 2.34 (m, 1H), 2.25 – 2.22 (m, 2H), 2.03 – 1.99 (m, 1H), 1.89 – 1.87 (m, 2H), 1.64 (s, 3H), 1.49 (s, 3H). [13]C NMR (126 MHz, MeOD, mixture of diastereomers) δ 176.6, 176.2, 173.2, 172.3, 171.6, 171.2, 161.0, 155.5, 150.0, 148.5, 140.4, 140.3, 139.1, 131.7, 130.3, 129.9, 129.8, 129.6, 127.4, 126.3, 125.5, 124.0, 115.2, 114.2, 61.5, 59.8, 58.7, 58.4, 56.4, 55.7, 42.0, 41.7, 36.3, 36.2, 32.5, 32.0, 30.9, 30.7, 26.5, 25.2. MS (ESI): *m/z* calcd for $C_{28}H_{31}N_3O_5$ $[M]^+$: 489.23; found $[M\text{-}H]^+$: 488.20, HRMS (ESI): *m/z* calcd for $C_{28}H_{32}O_5N_3$ $[M+H]^+$: 490.23365; found 490.23364.

4-(3-bromo-N-((*R*)-1-(4-methoxyphenyl)ethyl)benzamido)-5-oxo-5-(phenethylamino)-pentanoic acid (16b)



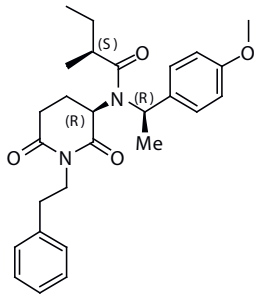
Obtained using procedure B; yield 65% (0.28 mmol, 160 mg), green oil. [1]H NMR (500 MHz, MeOD, mixture of diastereomers) δ 8.03 (d, *J* = 11.7 Hz, 2H), 7.82 (dd, *J* = 12.9, 7.9 Hz, 2H), 7.68 – 7.64 (m, 3H), 7.44 – 7.41 (m, 2H), 7.36 (td, *J* = 7.9, 3.0 Hz, 2H), 7.31 – 7.12 (m, 16H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.57 (dd, *J* = 9.3, 4.3 Hz, 1H), 4.51 (dd, *J* = 8.7, 5.5 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.51 – 3.46 (m, 2H), 3.42 – 3.35 (m, 3H), 2.85 – 2.73 (m, 5H), 2.39 – 2.32 (m, 4H), 2.30 – 2.26 (m, 1H), 2.14 – 2.09 (m, 2H), 2.03 – 1.99 (m, 1H), 1.40 (s, 3H), 1.27 (s, 3H). [13]C NMR (126 MHz, MeOD, mixture of diastereomers) δ 176.6, 174.9, 173.6, 168.5, 168.4, 140.4, 140.3, 137.3, 137.2, 135.7, 133.8, 131.9, 131.7, 131.6, 131.4, 131.3, 130.1, 129.9, 129.8, 129.6, 129.5, 129.4, 127.3, 125.9, 123.8, 123.4, 115.2, 59.0, 55.8, 55.1, 54.1, 42.0, 41.9, 36.4, 36.2, 33.5, 33.0, 31.4, 30.7, 28.1, 27.2. MS (ESI): *m/z* calcd for $C_{29}H_{31}BrN_2O_5$ $[M]^+$: 566.14; found $[M+Na]^+$:589.14; found $[M\text{-}H]^+$: 565.19, HRMS (ESI): *m/z* calcd for $C_{29}H_{32}O_5N_2Br[M+H]^+$: 567.14891; found 567.14905.

(*S*)-N-((*S*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methyl butanamide (3c-i)



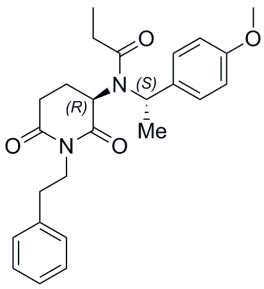
Obtained using procedure C, on 0.63 mmol scale; yield 74% (0.47 mmol, 212 mg), diastereomeric ratio (3c-i : 3c-ii) : 2:3 after separation, diastereomer I (3c-i) white solid, 82 mg; m.p. 128-130°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 6H), 7.21 – 7.18 (m, 1H), 6.92 (dd, *J* = 9.3, 2.4 Hz, 2H), 5.35 (q, *J* = 6.8 Hz, 1H), 4.01 – 3.91 (m, 2H), 3.83 (s, 3H), 3.38 – 3.30 (m, 1H), 2.89 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.86 – 2.78 (m, 2H), 2.62 – 2.42 (m, 2H), 2.15 – 2.07 (m, 2H), 1.90 – 1.81 (m, 1H), 1.69 (d, *J* = 6.9 Hz, 3H), 1.56 – 1.49 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 171.1, 170.4, 159.3, 139.0, 131.4, 129.0, 128.8, 128.7, 128.3, 126.2, 114.1, 55.3, 55.0, 54.5, 41.6, 37.5, 33.8, 31.8, 27.5, 21.6, 17.7, 17.6, 12.3. MS (ESI): *m/z* calcd for $C_{27}H_{34}N_2O_4$ $[M]^+$: 450.25 ; found $[M+Na]^+$: 473.27; $[M+K]^+$: 489.21, HRMS (ESI): *m/z* calcd for $C_{27}H_{35}O_4N_2$ $[M+H]^+$: 451.25913; found 451.25903, *m/z* calcd for $C_{27}H_{34}O_4N_2Na$ $[M+Na]^+$: 473.24108; found 473.24103.

(*S*)-N-((*R*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methyl butanamide (3c-ii)



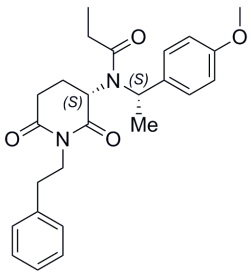
Obtained using procedure C, on 0.63 mmol scale; yield 74% (0.47 mmol, 212 mg), diastereomeric ratio (3c-i : 3c-ii) : 2:3 after separation, diasteromer II (3c-ii) white solid, 130 mg; m.p. 135-136°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.23 – 7.11 (m, 5H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.37 (q, *J* = 6.6 Hz, 1H), 3.94 – 3.90 (m, 2H), 3.82 (s, 3H), 3.42 – 3.41 (m, 1H), 2.87 – 2.69 (m, 5H), 2.39 – 2.30 (m, 1H), 1.90 – 1.83 (m, 2H), 1.67 (d, *J* = 6.9 Hz, 3H), 1.55 – 1.47 (m, 1H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 170.9, 168.9, 159.3, 139.0, 130.7, 129.0, 128.2, 126.1, 113.9, 55.3, 54.8, 54.6, 41.4, 37.6, 33.7, 31.8, 27.6, 22.9, 20.0, 17.8, 12.0. MS (ESI): *m/z* calcd for $C_{27}H_{34}N_2O_4$ $[M]^+$: 450.25 ; found $[M+Na]^+$: 473.21; $[M+K]^+$: 489.21, HRMS (ESI): *m/z* calcd for $C_{27}H_{34}O_4N_2Na$ $[M+Na]^+$: 473.24108; found 473.24112.

N-((*R*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*S*)-1-(4-methoxyphenyl)ethyl) propionamide (4c-i)



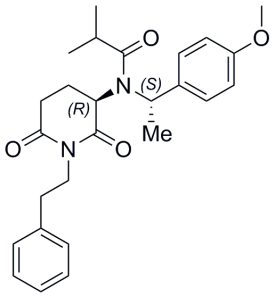
Obtained using procedure C, on 1.04 mmol scale; yield 41% (0.426 mmol, 180 mg), diastereomeric ratio (4c-i : 4c-ii) : 5:4 after separation, diastereomer I (4c-i) white solid, 100 mg; m.p. 172-173°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 6H), 7.22 – 7.16 (m, 1H), 6.94 – 6.88 (m, 2H), 5.23 (q, *J* = 6.7 Hz, 1H), 3.98 – 3.94 (m, 2H), 3.83 (s, 3H), 3.35 (dd, *J* = 10.5, 4.7 Hz, 1H), 2.81 (dd, *J* = 9.4, 6.8 Hz, 2H), 2.70 – 2.43 (m, 4H), 2.15 – 2.08 (m, 1H), 1.67 (d, *J* = 6.9 Hz, 3H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.10 – 1.03 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 171.1, 170.6, 159.3, 138.9, 131.1, 129.0, 128.7, 128.2, 126.1, 114.0, 55.3, 54.9, 54.7, 41.6, 33.8, 31.8, 26.8, 21.5, 17.0, 9.2. MS (ESI): *m/z* calcd for $C_{25}H_{30}N_2O_4$ $[M]^+$: 422.22; found $[M-H]^+$: 421.23; found $[M+Na]^+$: 445.30; $[M+K]^+$: 461.17, HRMS (ESI): *m/z* calcd for $C_{25}H_{30}O_4N_2Na$ $[M+Na]^+$: 445.20978; found 445.20969.

N-((*S*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*S*)-1-(4-methoxyphenyl)ethyl) propionamide (4c-ii)



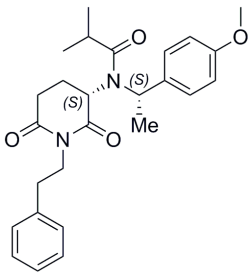
Obtained using procedure C, on 1.04 mmol scale; yield 41% (0.426 mmol, 180 mg), diastereomeric ratio (4c-i : 4c-ii) : 5:4 after separation, diastereomer II (4c-ii) white solid, 80 mg; m.p. 120-122°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.7 Hz, 2H), 7.24 – 7.13 (m, 5H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.25 (q, *J* = 6.5 Hz, 1H), 3.92 – 3.87 (m, 2H), 3.80 (s, 3H), 3.42 – 3.41 (m, 1H), 2.79 – 2.69 (m, 4H), 2.64 – 2.58 (m, 1H), 2.54 – 2.48 (m, 1H), 2.36 (ddd, *J* = 16.8, 14.9, 5.4 Hz, 1H), 1.87 – 1.83 (m, 1H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 170.9, 168.9, 159.2, 138.9, 130.5, 129.0, 128.9, 128.2, 127.3, 126.1, 113.8, 55.2, 54.8, 54.6, 41.5, 33.7, 31.8, 27.0, 22.9, 19.4, 9.3. MS (ESI): *m/z* calcd for $C_{25}H_{30}N_2O_4$ $[M]^+$:422.22; found $[M-H]^+$:421.23; found $[M+Na]^+$: 445.23; $[M+K]^+$: 461.30, HRMS (ESI): *m/z* calcd for $C_{25}H_{31}O_4N_2$ $[M+H]^+$: 423.22783; found 423.2275, *m/z* calcd for $C_{25}H_{30}O_4N_2Na$ $[M+Na]^+$: 445.20978; found 445.20969.

N-((*R*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*S*)-1-(4methoxyphenyl)ethyl) isobutyramide (5c-i)



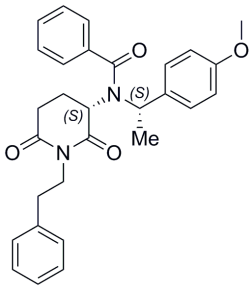
Obtained using procedure C, on 0.55 mmol scale; yield 53% (0.29 mmol, 126 mg), diastereomeric ratio (5c-i : 5c-ii) : 2:3 after separation, diastereomer I (5c-i) white solid, 50 mg; m.p. 119-121°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 6H), 7.25 – 7.20 (m, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.32 (q, *J* = 6.6 Hz, 1H), 4.03 – 3.93 (m, 2H), 3.85 (s, 3H), 3.37 – 3.36 (m, 1H), 3.09 – 3.04 (m, 1H), 2.86 – 2.80 (m, 2H), 2.58 – 2.43 (m, 2H), 2.13 (ddd, *J* = 16.4, 14.3, 5.4 Hz, 1H), 1.72 (d, *J* = 6.9 Hz, 3H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.11 – 1.05 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 171.1, 170.5, 159.3, 139.0, 131.2, 129.0, 128.7, 128.4, 128.2, 126.1, 114.0, 55.3, 54.9, 54.5, 41.6, 33.8, 31.8, 30.5, 21.5, 20.0, 19.3, 17.6. MS (ESI): *m/z* calcd for $C_{26}H_{32}N_2O_4$ $[M]^+$: 436.24; found $[M-H]^+$:435.15; found $[M+Na]^+$:459.22; $[M+K]^+$: 475.2, HRMS (ESI): *m/z* calcd for $C_{26}H_{33}O_4N_2$ $[M+H]^+$: 437.24348; found 437.24353, *m/z* calcd for $C_{26}H_{32}O_4N_2Na$ $[M+Na]^+$: 459.22543; found 459.2254.

N-((*S*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*S*)-1-(4-methoxyphenyl)ethyl) isobutyramide (5c-ii)



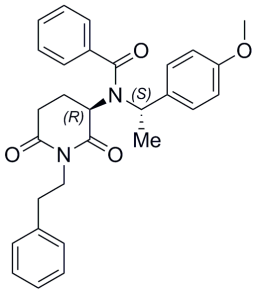
Obtained using procedure C, on 0.55 mmol scale; yield 53% (0.29 mmol, 126 mg), diastereomeric ratio (5c-i : 5c-ii) : 2:3 after separation, diastereomer II (5c-ii) white solid, 76 mg; m.p. 142-144°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.23 – 7.13 (m, 5H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.30 (q, *J* = 6.7 Hz, 1H), 3.91 (dd, *J* = 9.1, 7.2 Hz, 2H), 3.81 (s, 3H), 3.41 – 3.40 (m, 1H), 2.97 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.78 – 2.70 (m, 4H), 2.34 (ddd, *J* = 16.9, 14.9, 5.4 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.67 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 170.9, 168.7, 159.2, 138.9, 130.6, 128.9, 128.1, 126.0, 113.8, 55.2, 54.7, 54.6, 41.4, 33.6, 31.7, 30.6, 22.8, 19.9, 19.7, 19.5. MS (ESI): *m/z* calcd for $C_{26}H_{32}N_2O_4$ $[M]^+$: 436.24; found $[M-H]^+$: 435.28; found $[M+Na]^+$: 459.22; $[M+K]^+$: 475.35, HRMS (ESI): *m/z* calcd for $C_{26}H_{33}O_4N_2$ $[M+H]^+$: 437.24348; found 437.24344, *m/z* calcd for $C_{26}H_{32}O_4N_2Na$ $[M+Na]^+$: 459.22543; found 459.22528.

N-((*S*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*S*)-1-(4-methoxyphenyl)ethyl)benzamide (6c-i)



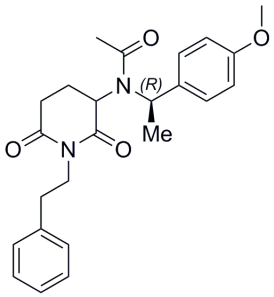
Obtained using procedure C, on 0.80 mmol scale; yield 45% (0.36 mmol, 170 mg), diastereomeric ratio (6c-i : 6c-ii) : 1:5 after separation, diastereomer I (6c-i) red oil, 26.5 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.7, 1.3 Hz, 2H), 7.51 – 7.43 (m, 3H), 7.33 – 7.27 (m, 4H), 7.21 – 7.18 (m, 3H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.09 (q, *J* = 6.8 Hz, 1H), 4.07 – 3.95 (m, 2H), 3.82 (s, 3H), 3.54 (dd, *J* = 11.7, 5.6 Hz, 1H), 2.86 – 2.82 (m, 2H), 2.70 – 2.58 (m, 2H), 2.20 (ddd, *J* = 16.9, 14.3, 5.4 Hz, 1H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.13 – 1.09 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 170.6, 170.1, 159.3, 138.9, 136.3, 131.2, 129.5, 129.0, 128.8, 128.5, 128.3, 126.2, 126.0, 114.0, 56.3, 55.3, 54.8, 41.7, 33.9, 31.9, 21.5, 16.9. MS (ESI): *m/z* calcd for $C_{29}H_{30}N_2O_4$ $[M]^+$: 470.22; found $[M-H]^+$: 469.24; found $[M+Na]^+$: 493.24; $[M+K]^+$: 509.25; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}O_4N_2Na$ $[M+Na]^+$: 493.20978; found 493.2103.

N-((*R*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*S*)-1-(4-methoxyphenyl)ethyl)benzamide (6c-ii)



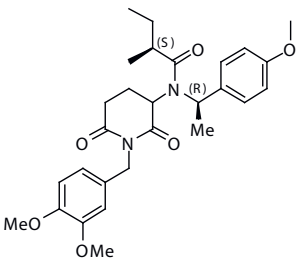
Obtained using procedure C, on 0.80 mmol scale; yield 45 % (0.36 mmol, 170 mg), diastereomeric ratio (6c-i : 6c-ii) : 1:5 after separation, diastereomer II (6c-ii) white solid, 143.5 mg, mp 190 – 192°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.2, 2.6 Hz, 2H), 7.49 – 7.42 (m, 5H), 7.29 – 7.23 (m, 4H), 7.19 – 7.14 (m, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.19 (q, *J* = 6.7 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.82 (s, 3H), 3.59 – 3.58 (m, 1H), 3.02 – 2.92 (m, 1H), 2.86 – 2.74 (m, 3H), 2.52 – 2.34 (m, 1H), 2.07 – 1.95 (m, 1H), 1.59 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 170.0, 168.5, 159.3, 138.9, 136.1, 130.3, 129.6, 129.0, 128.9, 128.7, 128.2, 126.1, 126.0, 113.9, 56.6, 55.2, 54.5, 41.5, 33.7, 31.9, 22.9, 19.6. MS (ESI): *m/z* calcd for $C_{29}H_{30}N_2O_4$ $[M]^+$: 470.22; found $[M-H]^+$: 469.11; found $[M+Na]^+$: 493.24; $[M+K]^+$: 509.37, HRMS (ESI): *m/z* calcd for $C_{29}H_{30}O_4N_2Na$ $[M+Na]^+$: 493.20978; found 493.21008.

N-(2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)acetamide (7c)



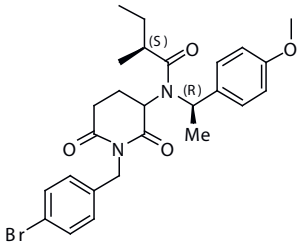
Obtained using procedure C, on 0.70 mmol scale; yield 62% (0.44 mmol, 177 mg), white semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.51 (d, *J* = 8.7Hz, 2H), 7.32 – 7.30 (m, 8H), 7.28 – 7.27 (m, 1H), 7.26 – 7.18 (m, 3H), 7.01 – 6.94 (m, 4H), 5.25 – 5.21 (m, 2H), 4.01 (td, *J* = 7.6, 4.4 Hz, 2H), 3.98 – 3.91 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.56 – 3.35 (m, 2H), 2.89 – 2.74 (m, 6H), 2.62 – 2.39 (m, 3H), 2.37 (s, 3H), 2.34 (s, 3H), 2.21 – 2.12 (m, 1H), 1.97 – 1.86 (m, 1H), 1.71 (dd, *J* = 13.3, 7.0 Hz, 6H), 1.14 – 1.05 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 171.0, 170.4, 169.4, 169.3, 168.7, 159.3, 159.2, 138.8, 130.9, 130.3, 128.9, 128.8, 128.6, 128.2, 128.1, 126.0, 114.0, 113.7, 56.1, 56.0, 55.2, 55.1, 54.7, 54.5, 41.5, 41.3, 33.8, 33.6, 31.7, 31.6, 22.7, 22.1, 22.0, 21.4, 19.2, 16.9. MS (ESI): *m/z* calcd for $C_{24}H_{28}N_2O_4$ $[M]^+$: 408.20; found $[M+Na]^+$: 431.37; $[M+K]^+$: 447.12, HRMS (ESI): *m/z* calcd for $C_{24}H_{29}O_4N_2$ $[M+H]^+$: 409.21218; found 409.21173, *m/z* calcd for $C_{24}H_{28}O_4N_2Na$ $[M+Na]^+$: 431.19413; found 431.19397.

(2*S*)-N-(1-(3,4-dimethoxybenzyl)-2,6-dioxopiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl) ethyl)-2-methylbutanamide (8c)



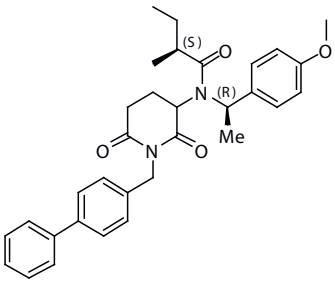
Obtained using procedure C, on 0.62 mmol scale; yield 20% (0.124 mmol, 62 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.50 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 2.6 Hz, 2H), 7.05 (d, *J* = 1.6 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.93 – 6.86 (m, 5H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 5.41 – 5.33 (m, 2H), 5.03 (d, *J* = 13.8 Hz, 1H), 4.93 (d, *J* = 13.9 Hz, 1H), 4.71 (dd, *J* = 15.6, 14.1 Hz, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 6H), 3.79 (s, 3H), 3.47 – 3.39 (m, 2H), 2.93 – 2.81 (m, 2H), 2.76 – 2.70 (m, 1H), 2.57 – 2.36 (m, 4H), 2.16 – 2.06 (m, 1H), 1.89 – 1.80 (m, 3H), 1.71 (d, *J* = 6.9 Hz, 3H), 1.67 (d, *J* = 7.0 Hz, 3H), 1.55 – 1.48 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.93 – 0.81 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 175.4, 175.1, 171.2, 170.9, 170.7, 169.2, 159.2, 148.7, 148.0, 147.9, 131.2, 130.6, 130.0, 129.9, 129.0, 128.9, 128.6, 121.3, 121.2, 114.0, 113.7, 112.2, 111.9, 110.5, 110.4, 55.8, 55.6, 55.3, 55.0, 54.8, 54.5, 54.4, 43.3, 43.2, 37.5, 31.8, 29.6, 27.6, 21.5, 17.8, 17.6, 12.2, 12.0. MS (ESI): *m/z* calcd for $C_{28}H_{36}N_2O_6$ $[M]^+$: 496.26; found $[M-H]^+$:495.26; found $[M+Na]^+$: 519.39; $[M+K]^+$: 535.33.

(2*S*)-N-(1-(4-bromobenzyl)-2,6-dioxopiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamide (9c)



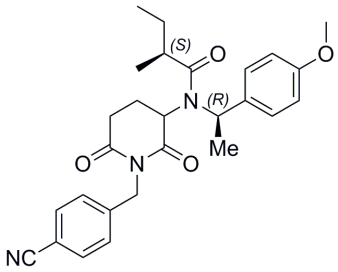
Obtained using procedure C, on 0.45 mmol scale; yield 52% (0.234 mmol, 121 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.47 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.28 – 7.25 (m, 4H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.93 – 6.87 (m, 4H), 5.45 – 5.26 (m, 2H), 4.96 (d, *J* = 14.1 Hz, 1H), 4.87 (d, *J* = 14.1 Hz, 1H), 4.74 (t, *J* = 14.2 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.50 – 3.34 (m, 2H), 2.90 – 2.70 (m, 4H), 2.54 – 2.36 (m, 3H), 2.11 (ddd, *J* = 15.4, 13.6, 4.5 Hz, 1H), 1.91 – 1.78 (m, 3H), 1.68 (d, *J* = 6.9 Hz, 3H), 1.65 (d, *J* = 7.0 Hz, 3H), 1.56 – 1.45 (m, 2H), 1.27- 1.26 (m, 1H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.05 – 0.98 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 175.6, 175.3, 171.1, 170.9, 170.6, 169.2, 159.2, 136.3, 136.1, 131.1, 130.6, 130.5, 130.4, 129.0, 128.8, 128.6, 121.1, 121.0, 114.0, 113.7, 55.2, 55.1, 54.9, 54.7, 54.5, 54.4, 43.0, 42.8, 37.5, 37.4, 31.7, 27.5, 22.7, 22.6, 21.5, 19.8, 17.7, 17.5, 12.2, 11.9. MS (ESI): *m/z* calcd for $C_{26}H_{31}BrN_2O_4$ $[M]^+$:514.15; found $[M-H]^+$:513.15; found $[M+Na]^+$: 537.22; $[M+K]^+$: 553.24.

(2*S*)-N-(1-([1,1'-biphenyl]-4-ylmethyl)-2,6-dioxopiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl) ethyl)-2-methylbutanamide (10c)



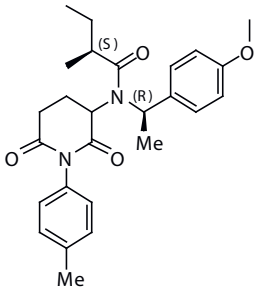
Obtained using procedure C, on 0.40 mmol scale; yield 72% (0.288 mmol, 148 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.57 – 7.55 (m, 4H), 7.53 – 7.46 (m, 8H), 7.43 – 7.36 (m, 7H), 7.34 – 7.28 (m, 3H), 6.94 – 6.90 (m, 4H), 5.38 – 5.37 (m, 2H), 5.08 (d, *J* = 14.0 Hz, 1H), 4.99 (d, *J* = 14.1 Hz, 1H), 4.90 (t, *J* = 13.4 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.49 – 3.43 (m, 2H), 2.95 – 2.72 (m, 4H), 2.58 – 2.50 (m, 2H), 2.47 – 2.39 (m, 1H), 2.23 – 2.11 (m, 1H), 1.92 – 1.84 (m, 3H), 1.71 (d, *J* = 6.8 Hz, 3H), 1.67 (d, *J* = 6.9 Hz, 3H), 1.57 – 1.50 (m, 2H), 1.31-1.29 (m, 1H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.04 (dt, *J* = 14.4, 7.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 175.7, 175.3, 171.2, 171.0, 170.6, 169.1, 159.2, 140.9, 139.9, 139.8, 136.4, 136.3, 131.2, 130.6, 129.2, 128.9, 128.6, 128.5, 127.0, 126.9, 126.8, 114.0, 113.7, 55.2, 55.1, 55.0, 54.8, 54.6, 54.5, 43.3, 43.2, 37.6, 37.5, 31.8, 27.5, 22.8, 21.6, 19.9, 17.7, 17.5, 12.2, 11.9. MS (ESI): *m/z* calcd for $C_{32}H_{36}N_2O_4$ $[M]^+$: 512.27; found $[M-H]^+$: 511.26; found $[M+Na]^+$: 535.27; $[M+K]^+$: 551.27, HRMS (ESI): *m/z* calcd for $C_{32}H_{37}O_4N_2$ $[M+H]^+$: 513.27478; found 513.27472, *m/z* calcd for $C_{32}H_{36}O_4N_2Na$ $[M+Na]^+$: 535.25673; found 535.25659.

(2*S*)-N-(1-(4-cyanobenzyl)-2,6-dioxopiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamide (11c)



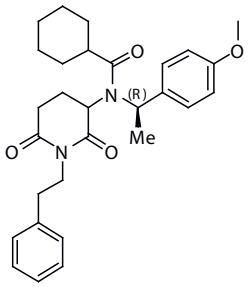
Obtained using procedure C, on 0.40 mmol scale; yield 94% (0.376 mmol, 173 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.52 – 7.50 (m, 2H), 7.50 – 7.43 (m, 6H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.24 (m, 2H), 6.89 – 6.86 (m, 4H), 5.35 (dd, *J* = 6.6, 3.5 Hz, 2H), 5.04 (d, *J* = 14.5 Hz, 1H), 4.95 (d, *J* = 14.6 Hz, 1H), 4.79 (dd, *J* = 19.8, 14.5 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.53 – 3.42 (m, 2H), 2.89 – 2.71 (m, 4H), 2.55 – 2.40 (m, 3H), 2.19 – 2.11 (m, 1H), 1.93 – 1.77 (m, 3H), 1.66 (dd, *J* = 8.8, 7.2 Hz, 6H), 1.54 – 1.45 (m, 2H), 1.25- 1.24 (m, 1H), 1.15 (dd, *J* = 14.4, 6.8 Hz, 6H), 0.98 (td, *J* = 7.4, 4.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 175.6, 175.3, 171.0, 170.9, 170.7, 169.2, 159.2, 159.1, 142.5, 142.4, 131.9, 131.8, 131.0, 130.4, 129.0, 128.9, 128.6, 118.8, 113.9, 113.6, 110.6, 55.1, 54.8, 54.5, 54.4, 43.2, 43.1, 37.4, 37.3, 31.4, 27.4, 22.5, 21.4, 19.7, 17.7, 17.6, 17.4, 12.1, 11.7. MS (ESI): *m/z* calcd for $C_{27}H_{31}N_3O_4$ $[M]^+$: 461.23; found $[M-H]^+$: 460.10; found $[M+Na]^+$:484.23; $[M+K]^+$: 500.24, HRMS (ESI): *m/z* calcd for $C_{27}H_{32}O_4N_3$ $[M+H]^+$: 462.23873; found 462.23874, *m/z* calcd for $C_{27}H_{31}O_4N_3Na$ $[M+Na]^+$: 484.22068; found 484.2207.

(2*S*)-N-(2,6-dioxo-1-(p-tolyl)piperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylbutanamide (12c)



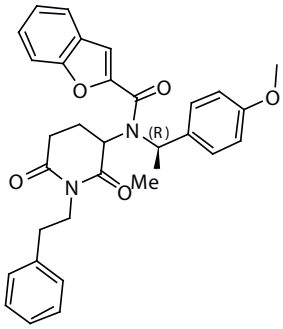
Obtained using procedure C, on 0.374 mmol scale; yield 31% (0.116 mmol, 51 mg), colourless semi-solid.^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.52 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.24 (t, *J* = 10.3 Hz, 4H), 7.09 (d, *J* = 6.8 Hz, 4H), 6.97 (d, *J* = 8.2 Hz, 3H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.39 (ABq, *J* = 6.5 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.57 (dd, *J* = 10.6, 5.6 Hz, 2H), 3.00 – 2.81 (m, 3H), 2.73 – 2.59 (m, 4H), 2.37 (d, *J* = 7.2 Hz, 6H), 2.04 – 2.01 (m, 1H), 1.92 – 1.84 (m, 2H), 1.72 (dd, *J* = 12.0, 7.0 Hz, 6H), 1.61- 1.49 (m, 3H), 1.36 – 1.28 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H), 1.06 (t, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 175.8, 175.5, 171.3, 171.2, 169.6, 159.6, 159.1, 138.1, 138.0, 133.0, 132.9, 131.3, 130.7, 129.8, 129.7, 129.0, 128.7, 128.0, 114.0, 113.8, 55.3, 55.2, 54.9, 54.6, 37.4, 32.0, 27.6, 27.5, 22.3, 21.7, 21.2, 20.0, 17.8, 17.7, 17.5, 12.3, 11.9. MS (ESI): *m/z* calcd for $C_{26}H_{32}N_2O_4$ $[M]^+$: 436.24; found $[M-H]^+$: 435.15; found $[M+Na]^+$: 459.28; $[M+K]^+$: 475.22, HRMS (ESI): *m/z* calcd for $C_{26}H_{33}O_4N_2$ $[M+H]^+$: 437.24348; found 437.2435, *m/z* calcd for $C_{26}H_{32}O_4N_2Na$ $[M+Na]^+$: 459.22543; found 459.22534.

N-(2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)cyclohexane-carboxamide (13c)



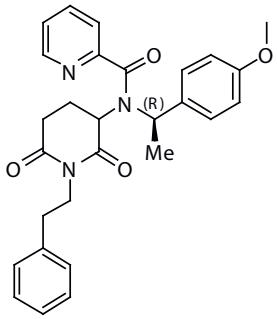
Obtained using procedure C, on 0.22 mmol scale; yield 67% (0.147 mmol, 70 mg), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.50 (d, *J* = 8.7 Hz, 2H), 7.31 – 7.27 (m, 4H), 7.25 – 7.12 (m, 8H), 6.93 (dd, *J* = 11.8, 8.7 Hz, 4H), 5.30 – 5.29 (m, 2H), 4.03 – 3.89 (m, 4H), 3.83 (s, 3H), 3.81 (s, 3H), 3.39 – 3.34 (m, 2H), 2.86 – 2.63 (m, 9H), 2.62 – 2.45 (m, 2H), 2.38 – 2.30 (m, 2H), 2.14 – 2.10 (m, 1H), 1.98 – 1.79 (m, 8H), 1.73 – 1.58 (m, 10H), 1.40 – 1.22 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 175.0, 174.9, 171.0, 170.9, 170.4, 168.8, 159.2, 138.9, 131.2, 130.7, 128.9, 128.6, 128.2, 128.1, 126.1, 126.0, 113.9, 113.7, 55.3, 55.2, 55.1, 54.9, 54.7, 54.5, 54.3, 41.5, 41.4, 41.0, 40.9, 33.8, 33.7, 31.7, 29.6, 29.3, 25.7, 22.9, 22.8, 21.5, 20.0, 17.6. MS (ESI): *m/z* calcd for $C_{29}H_{36}N_2O_4$ $[M]^+$: 476.27; found $[M+Na]^+$: 499.23; $[M+K]^+$: 515.36.

N-(2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)benzofuran-2-carboxamide (14c)



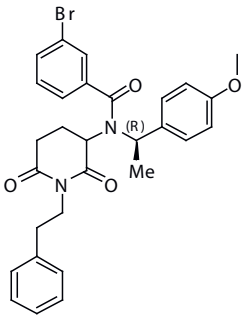
Obtained using procedure C, on 0.34 mmol scale; yield 46% (0.156 mmol, 80 mg), red oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.69 – 7.65 (m, 2H), 7.57 – 7.51 (m, 4H), 7.46 – 7.39 (m, 6H), 7.33 – 7.32 – 7.27 (m, 6H), 7.22 – 7.18 (m, 6H), 6.94 (t, *J* = 9.1 Hz, 4H), 6.00 - 5.98 (m, 2H), 4.09 – 4.01 (m, 1H), 3.99 – 3.91 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.67 – 3.57 (m, 2H), 2.95 – 2.74 (m, 7H), 2.66 – 2.54 (m, 2H), 2.47 – 2.41 (m, 1H), 2.22 – 2.14 (m, 1H), 2.10 – 1.94 (m, 1H), 1.77 (dd, *J* = 15.6, 6.9 Hz, 6H), 1.14 – 1.12 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 170.9, 170.7, 169.8, 168.1, 160.2, 159.9, 159.3, 154.6, 148.7, 148.6, 138.8, 138.7, 130.7, 130.1, 129.3, 129.0, 128.9, 128.5, 128.4, 128.2, 126.8, 126.6, 126.2, 126.1, 123.7, 122.3, 114.0, 113.7, 112.3, 111.9, 55.7, 55.5, 55.4, 55.3, 55.2, 51.3, 41.7, 41.5, 33.8, 33.6, 31.7, 29.6, 22.8, 21.3, 19.6, 17.4. MS (ESI): *m/z* calcd for $C_{31}H_{30}N_2O_5$ $[M]^+$:510.22; found $[M-H]^+$: 509.25; found $[M+Na]^+$: 533.25; $[M+K]^+$: 549.19, HRMS (ESI): *m/z* calcd for $C_{31}H_{30}O_5N_2Na$ $[M+Na]^+$: 533.20469; found 533.20483.

N-(2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl)picolinamide (15c)



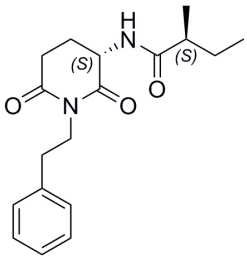
Obtained using procedure C, on 0.38 mmol scale; yield 55% (0.21 mmol, 98 mg), white semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 8.67 (d, *J* = 15.8 Hz, 2H), 7.90 – 7.82 (m, 2H), 7.74 (t, *J* = 6.9 Hz, 2H), 7.57 – 7.48 (m, 4H), 7.39 (d, *J* = 3.6 Hz, 2H), 7.30 – 7.29 (m, 4H), 7.25 – 7.17 (m, 6H), 6.95 – 6.92 (m, 4H), 5.56 (dd, *J* = 11.9, 4.8 Hz, 2H), 4.09 – 4.02 (m, 1H), 3.98 – 3.96 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.68 – 3.53 (m, 2H), 2.98 – 2.80 (m, 7H), 2.66 – 2.62 (m, 2H), 2.50 – 2.44 (m, 1H), 2.27 – 2.16 (m, 1H), 2.08 – 2.06 (m, 2H), 1.71 (d, *J* = 2.9 Hz, 3H), 1.62 (d, *J* = 3.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 171.0, 170.8, 170.0, 168.2, 167.7, 159.2, 154.3, 154.2, 148.5, 138.9, 137.1, 131.2, 130.3, 129.4, 129.1, 129.0, 128.9, 128.2, 128.1, 126.2, 126.1, 124.5, 123.3, 113.8, 113.5, 56.1, 55.5, 55.2, 55.0, 41.6, 41.4, 33.8, 33.6, 31.8, 31.7, 22.6, 21.7, 18.9, 16.9. MS (ESI): *m/z* calcd for $C_{28}H_{29}N_3O_4$ $[M]^+$: 471.22; found $[M+Na]^+$: 494.19; $[M+K]^+$: 510.19, HRMS (ESI): *m/z* calcd for $C_{28}H_{30}O_4N_3$ $[M+H]^+$: 472.22308; found 472.22321, *m/z* calcd for $C_{28}H_{29}O_4N_3Na$ $[M+Na]^+$: 494.20503; found 494.20508.

3-bromo-N-(2,6-dioxo-1-phenethylpiperidin-3-yl)-N-((*R*)-1-(4-methoxyphenyl)ethyl) benzamide (16c)



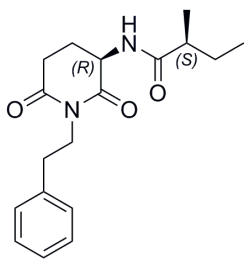
Obtained using procedure C, on 0.21 mmol scale; yield 17% (0.036 mmol, 20 mg), yellow oil. NMR indicates one diastereomer.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 1.4 Hz, 1H), 7.63 (dd, *J* = 4.8, 3.9 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.31 (m, 4H), 7.25 – 7.21 (m, 3H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.06 (ABq, *J* = 6.8 Hz, 1H), 4.11 – 3.97 (m, 2H), 3.85 (s, 3H), 3.57 (dd, *J* = 11.8, 5.6 Hz, 1H), 2.87 (t, *J* = 8.0 Hz, 2H), 2.71 – 2.60 (m, 2H), 2.28 – 2.19 (m, 1H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.16 -1.11 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 169.9, 168.3, 159.4, 138.8, 138.1, 132.6, 130.8, 130.4, 129.1, 129.0, 128.5, 128.3, 126.2, 124.5, 123.0, 114.1, 56.5, 55.3, 54.9, 41.7, 33.9, 31.8, 21.4, 16.9. MS (ESI): *m/z* calcd for $C_{29}H_{29}BrN_2O_4$ $[M]^+$: 548.13; found $[M-H]^+$: 546.99; found $[M+Na]^+$: 573.13; $[M+K]^+$: 589.14.

(*S*)-N-((*S*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-2-methylbutanamide [julocrotine] (3d-i)



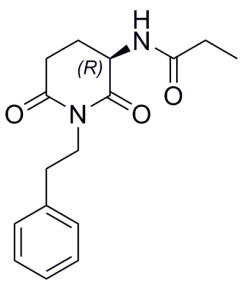
Obtained using procedure D, on 0.18mmol scale; yield 96% (0.175 mmol, 56 mg). Purification with column chromatography (PE:EA [0 to 100% EtOAc in PE]); white solid; m.p. 108-109°C (lit. 108-109 °C [S4]); [α]= – 7.85 (c= 0.28, $CHCl_3$), lit. = –9 $CHCl_3$ [S4]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 2H), 7.23 – 7.21 (m, 3H), 6.26 (d, *J* = 4.5 Hz, 1H), 4.48 (dt, *J* = 12.9, 5.2 Hz, 1H), 4.07 – 3.95 (m, 2H), 2.85 – 2.79 (m, 3H), 2.75 – 2.68 (m, 1H), 2.56 – 2.51 (m, 1H), 2.24 – 2.19 (m, 1H), 1.72 – 1.65 (m, 2H), 1.51 – 1.45 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 171.8, 170.9, 138.1, 128.9, 128.4, 126.5, 51.1, 42.9, 41.6, 33.9, 31.6, 27.2, 24.4, 17.3, 11.8. MS (ESI): *m/z* calcd for $C_{18}H_{24}N_2O_3$ $[M]^+$: 316.18; found 317.27, found $[M-H]^+$: 315.31; found $[M+Na]^+$: 339.26; $[M+K]^+$: 355.26**,** HRMS (ESI): *m/z* calcd for $C_{18}H_{25}O_3N_2$ $[M+H]^+$: 317.18597; found 317.18588.

(*S*)-N-((*R*)-2,6-dioxo-1-phenethylpiperidin-3-yl)-2-methylbutanamide (3d-ii)



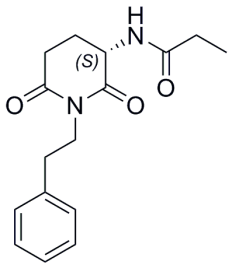
Obtained using procedure D, on 0.157 mmol scale; yield 83% (0.130 mmol, 41 mg). Purification with column chromatography (PE:EA [0 to 100% EtOAc in PE]); white solid; m.p. 107-108 °C; [α] = +11.81 (c= 0.22, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.23-7.21 (m, 3H), 6.28 (d, *J* = 4.8 Hz, 1H), 4.48 (dt, *J* = 12.9, 5.2 Hz, 1H), 4.06-3.95 (m, 2H), 2.84-2.79 (m, 3H), 2.75 – 2.68 (m, 1H), 2.57 – 2.52 (m, 1H), 2.25-2.18 (m, 1H), 1.71 – 1.65 (m, 2H), 1.51 – 1.45 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7, 171.9, 170.9, 138.1, 128.9, 128.4, 126.6, 51.3, 42.9, 41.6, 33.9, 31.7, 27.3, 24.4, 17.2, 11.8. MS (ESI): *m/z* calcd for $C_{18}H_{24}N_2O_3$ $[M]^+$: 316.18; found 317.33, found $[M-H]^+$:315.12; found $[M+Na]^+$: 339.19; $[M+K]^+$: 355.07**,** HRMS (ESI): *m/z* calcd for $C_{18}H_{25}O_3N_2$ $[M+H]^+$: 317.18597; found 317.18591.

(*R*)-N-(2,6-dioxo-1-phenethylpiperidin-3-yl)propionamide (4d-i)



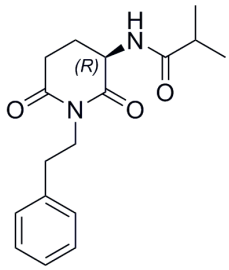
Obtained using procedure D, on 0.14 mmol scale; yield 82% (0.115 mmol, 32 mg). Purification with column chromatography (DCM : MeOH [0 to 10% MeOH in DCM]); white solid; m.p. 100-101 °C; [α] = +11.25 (c= 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.23-7.20 (m, 3H), 6.26 (b, 1H), 4.46 (dt, *J* = 12.7, 5.1 Hz, 1H), 4.07 – 3.95 (m, 2H), 2.81 (dd, *J* = 14.3, 6.0 Hz, 3H), 2.75-2.68 (m, 1H), 2.56 – 2.52 (m, 1H),), 2.30 (qd, *J* = 7.5, 2.5 Hz, 2H), 1.66 (dd, *J* = 13.1, 4.7 Hz, 1H), 1.19 (t, *J* = 7.6 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 171.8, 170.9, 138.1, 129.0, 128.5, 126.6, 51.4, 41.6, 33.9, 31.7, 29.5, 24.4, 9.6. MS (ESI): *m/z* calcd for $C_{16}H_{20}N_2O_3$ $[M]^+$: 288.15; found 289.16, found $[M+Na]^+$: 311.09; $[M+K]^+$: 327.22**,** HRMS (ESI): *m/z* calcd for $C_{16}H_{21}O_3N_2$ $[M+H]^+$: 289.15467; found 289.1546.

(*S*)-N-(2,6-dioxo-1-phenethylpiperidin-3-yl)propionamide [(*S*)-crotonimide A] (4d-ii)



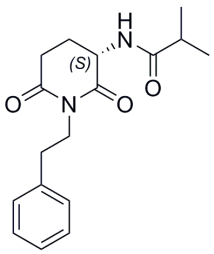
Obtained using procedure D, on 0.14mmol scale; yield 90% (0.125 mmol, 36 mg). Purification with column chromatography (DCM : MeOH [0 to 10% MeOH in DCM]); white solid; m.p. 100-101 °C (lit. 98.5 – 99.5 °C [S5], 101-102 °C [S6]); [α] = –10.30 (c = 0.36, $CHCl_3$), lit. = –9.2 (*c*= 0.10, $CHCl_3$)[S5], [α]= – 13.8 (*c* = 0.4, $CHCl_3$)[S6]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.23 – 7.20 (m, 3H), 6.26 (d, *J* = 4.2 Hz, 1H), 4.46 (dt, *J* = 13.0, 5.2 Hz, 1H), 4.07 – 3.95 (m, 2H), 2.85 – 2.79 (m, 3H), 2.75-2.67 (m, 1H), 2.57 – 2.51 (m, 1H), 2.30 (qd, *J* = 7.6, 2.5 Hz, 2H), 1.66 (dd, *J* = 13.2, 4.8 Hz, 1H), 1.19 (t, *J* = 7.6 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 171.8, 170.9, 138.1, 129.0, 128.4, 126.6, 51.4, 41.6, 33.9, 31.7, 29.5, 24.4, 9.6. MS (ESI): *m/z* calcd for $C_{16}H_{20}N_2O_3$ $[M]^+$: 288.15; found 289.10, found $[M+Na]^+$: 311.22; $[M+K]^+$: 327.22**,** HRMS (ESI): *m/z* calcd for $C_{16}H_{21}O_3N_2$ $[M+H]^+$: 289.15467; found 289.15457.

(*R*)-N-(2,6-dioxo-1-phenethylpiperidin-3-yl)isobutyramide (5d-i)



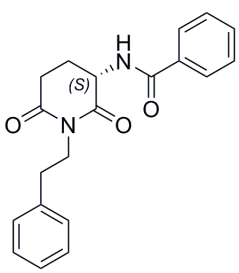
Obtained using procedure D, on 0.103 mmol scale; yield 90% (0.092 mmol, 28 mg). Purification with column chromatography(PE:EA [0 to 100% EtOAc in PE]); white solid; m.p. 127-129 °C; [α] = +10.41 (c= 0.73, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.22-7.20 (m, 3H), 6.33 (d, *J* = 4.9 Hz, 1H), 4.46 (dt, *J* = 12.9, 5.3 Hz, 1H), 4.06 – 3.93 (m, 2H), 2.84 – 2.78 (m, 3H), 2.74 – 2.66 (m, 1H), 2.53-2.48 (m, 1H), 2.46-2.42 (m, 1H), 1.65 (qd, *J* = 13.0, 5Hz, 1H), 1.19 (dd, *J* = 6.9, 3.8 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 171.9, 170.9, 138.1, 128.9, 128.4, 126.6, 51.2, 41.6, 35.4, 33.9, 31.6, 24.3, 19.5, 19.3. MS (ESI): *m/z* calcd for $C_{17}H_{22}N_2O_3$ $[M]^+$: 302.16; found 303.15, found $[M+Na]^+$: 325.33; $[M+K]^+$: 341.02, HRMS (ESI): *m/z* calcd for $C_{17}H_{23}O_3N_2$ $[M+H]^+$: 303.17032; found 303.17023.

(*S*)-N-(2,6-dioxo-1-phenethylpiperidin-3-yl)isobutyramide [(*S*)-crotonimide B] (5d-ii)



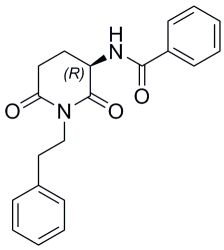
Obtained using procedure D, on 0.16 mmol scale; yield 82% (0.132 mmol, 40 mg). Purification with column chromatography (PE:EA [0 to 100% EtOAc in PE]); white solid; m.p. 127-128 °C (lit. 127.5-128.5 [S5], 126-127 °C[S6]); [α] = – 10.31 (c= 0.64, $CHCl_3$), lit. = –12.5 (*c* = 0.10, $CHCl_3$)[S5] , [α] = – 12.8 (*c* = 0.4, $CHCl_3$)[S6]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.23-7.21 (m, 3H), 6.33 (d, *J* = 4.0 Hz, 1H), 4.46 (dt, *J* = 12.7, 5.2 Hz, 1H), 4.07 – 3.95 (m, 2H), 2.83 – 2.80 (m, 3H), 2.75 – 2.67 (m, 1H), 2.55 – 2.50 (m, 1H), 2.49-2.43 (m, 1H), 1.67 (qd, *J* = 13.1, 4.7 Hz, 1H), 1.20 (dd, *J* = 6.8, 3.8 Hz, 6H) .^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 171.9, 170.9, 138.1, 128.9, 128.4, 126.6, 51.2, 41.6, 35.4, 33.9, 31.6, 24.3, 19.5, 19.3. MS (ESI): *m/z* calcd for $C_{17}H_{22}N_2O_3$ $[M]^+$: 302.16; found 303.22, found $[M-H]^+$: 301.32; found $[M+Na]^+$: 325.27; $[M+K]^+$: 341.08, HRMS (ESI): *m/z* calcd for $C_{17}H_{23}O_3N_2$ $[M+H]^+$: 303.17032; found 303.17023.

(*S*)-N-(2,6-dioxo-1-phenethylpiperidin-3-yl)benzamide [(*S*)-crotonimide C] (6d-i)



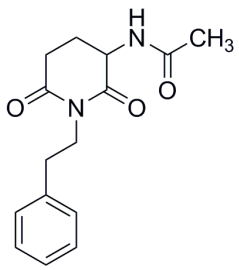
Obtained using procedure D, on 0.05mmol scale; yield 90% (0.047 mmol, 15 mg). Purification with column chromatography (PE:EA [0 to 100% EtOAc in PE]); white solid; m.p. 185-187 °C (lit. amorphous solid[S7]); [α] = –17.14 (c = 0.07, $CHCl_3$), lit. = –13.0 (*c*= 0.0009, $CHCl_3$)[S7]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.23 (d, *J* = 6.1 Hz, 3H), 7.04 (d, *J* = 4.3 Hz, 1H), 4.64 (dt, *J* = 12.8, 5.0 Hz, 1H), 4.11 – 3.99 (m, 2H), 2.89-2.84 (m, 3H), 2.83 – 2.77 (m, 1H), 2.74 – 2.69 (m, 1H), 1.79 (qd, *J* = 12.9, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 170.9, 167.5, 138.1, 133.5, 132.1, 129.0, 128.7, 128.5, 127.1, 126.6, 52.0, 41.7, 33.9, 31.7, 24.5. MS (ESI): *m/z* calcd for $C_{20}H_{20}N_2O_3$ $[M]^+$:336.15; found 337.18, $[M-H]^+$: 335.10; found $[M+Na]^+$: 359.23,HRMS (ESI): *m/z* calcd for $C_{20}H_{21}O_3N_2$ $[M+H]^+$: 337.15467; found 337.15466.

(*R*)-N-(2,6-dioxo-1-phenethylpiperidin-3-yl)benzamide (6d-ii)



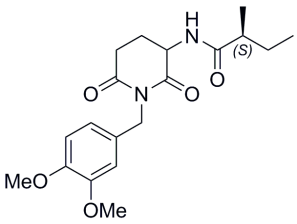
Obtained using procedure D, on 0.255mmol scale; yield 93% (0.238 mmol, 80 mg). Purification with column chromatography (PE: EA [0 to 100% EtOAc in PE]); white solid; m.p. 186-188 °C; [α] = +15.18 (c= 0.54, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.23 (d, *J* = 6.0 Hz, 3H), 7.06 (d, *J* = 4.5 Hz, 1H), 4.64 (dt, *J* = 12.9, 5.0 Hz, 1H), 4.10 – 3.99 (m, 2H), 2.89 – 2.83 (m, 3H), 2.81-2.75 (m, 1H), 2.72 – 2.67 (m, 1H), 1.78 (qd, *J* = 12.9, 5.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 170.9, 167.5, 138.0, 133.5, 132.0, 129.0, 128.7, 128.5, 127.1, 126.7, 51.9, 41.7, 33.9, 31.7, 24.4. MS (ESI): *m/z* calcd for $C_{20}H_{20}N_2O_3$ $[M]^+$:336.15; found 337.24, $[M-H]^+$: 335.10; found $[M+Na]^+$: 359.17, HRMS (ESI): *m/z* calcd for $C_{20}H_{21}O_3N_2$ $[M+H]^+$: 337.15467; found 337.1546.

N-(2,6-dioxo-1-phenethylpiperidin-3-yl)acetamide (7d)



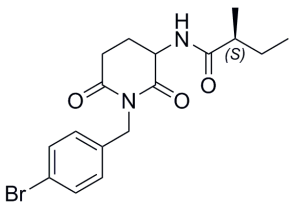
Obtained using procedure D, on 0.44 mmol scale; yield 85% (0.374 mmol, 102 mg). Purification with column chromatography (DCM : MeOH [0 to 10% MeOH in DCM]); yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 6.51 (d, *J* = 4.1 Hz, 1H), 4.48 (dt, *J* = 12.8, 5.4 Hz, 1H), 4.06 – 3.94 (m, 2H), 2.85 – 2.78 (m, 3H), 2.74-2.67 (m, 1H), 2.50-2.45 (m, 1H), 2.06 (s, 3H), 1.69 (qd, *J* = 13.0, 6.5 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 170.9, 170.4, 138.0, 128.8, 128.4, 126.5, 51.3, 41.5, 33.8, 31.5, 24.2, 23.0. MS (ESI): *m/z* calcd for $C_{15}H_{18}N_2O_3$ $[M]^+$: 274.13; found 275.11; found $[M+Na]^+$: 297.23, HRMS (ESI): *m/z* calcd for $C_{15}H_{19}O_3N_2$ $[M+H]^+$:275.13902; found 275.13901.

(2*S*)-N-(1-(3,4-dimethoxybenzyl)-2,6-dioxopiperidin-3-yl)-2-methylbutanamide (8d)



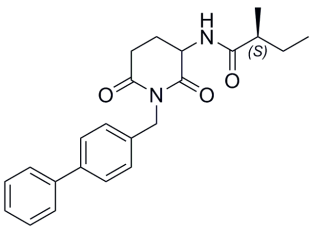
Obtained using procedure D, on 0.10 mmol scale; yield 75 % (0.075 mmol, 27 mg). Purification with column chromatography (PE : EA [0 to 100% EtOAc in PE]); brown oil.^{1}H NMR (500 MHz, $CDCl_3$, combined) δ 6.93 – 6.91 (m, 2H), 6.78 – 6.76 (m, 1H), 6.35 (b, 1H), 4.87 (ABq, *J* = 13.6 Hz, 2H), 4.53 – 4.51 (m, 1H), 3.85 – 3.84 (m, 6H), 2.88 – 2.76 (m, 2H), 2.53 – 2.52 (m, 1H), 2.20 – 2.19 (m, 1H), 1.73 - 1.69 (m, 2H), 1.46 – 1.45 (m, 1H), 1.15 (d, *J* = 3.8 Hz, 3H), 0.90 (dt, *J* = 6.6, 5.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, combined) δ 176.8, 172.0, 171.2, 148.7, 148.5, 129.3, 121.5, 112.5, 111.0, 110.8, 56.2, 55.6, 51.6, 51.1, 43.5, 42.8, 31.7, 27.5, 27.1, 24.5, 24.1, 23.9, 17.2, 11.8. MS (ESI): *m/z* calcd for $C_{19}H_{26}N_2O_5$ $[M]^+$:362.18; found 363.26; found $[M+Na]^+$: 385.25; found $[M+K]^+$: 401.19**,** HRMS (ESI): *m/z* calcd for $C_{19}H_{27}O_5N_2$ $[M+H]^+$: 363.19145; found 363.19135.

(2*S*)-N-(1-(4-bromobenzyl)-2,6-dioxopiperidin-3-yl)-2-methylbutanamide (9d)



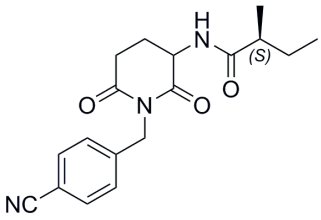
Obtained using procedure D, on 0.233 mmol scale; yield 98 % (0.228 mmol, 87 mg). Purification with column chromatography (PE: EA [0 to 100% EtOAc in PE]); red oil.^{1}H NMR (500 MHz, $CDCl_3$, combined) δ 7.39 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.20 (dd, *J* = 8.4, 2.0 Hz, 2H), 6.37 (d, *J* = 5.6 Hz, 1H), 4.85 (ABq, *J* = 15.0 Hz, 2H), 4.54 (dt, *J* = 12.6, 5.4 Hz, 1H),2.88 – 2.73 (m, 2H), 2.51 – 2.45 (m, 1H), 2.22 – 2.16 (m, 1H), 1.77 – 1.62 (m, 2H), 1.44 (ddd, *J* = 13.6, 7.6, 1.5 Hz, 1H), 1.13 (dd, *J* = 6.8, 1.9 Hz, 3H), 0.89 (ddd, *J* = 15.0, 8.1, 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, combined) δ 176.7, 176.6, 171.9, 171.0, 135.6, 131.6, 131.5, 130.5, 121.6, 51.2, 43.1, 42.8, 31.7, 27.4, 27.2, 24.2, 17.2, 17.1, 11.70. MS(ESI): *m/z* calcd for $C_{17}H_{21}BrN_2O_3$ $[M]^+$: 380.07; found 381.02; found $[M+K]^+$:419.09, HRMS (ESI): *m/z* calcd for $C_{17}H_{22}O_3N_2Br$ $[M+H]^+$: 381.08083; found 381.08093.

(2*S*)-N-(1-([1,1′-biphenyl]-4-ylmethyl)-2,6-dioxopiperidin-3-yl)-2-methylbutanamide (10d)



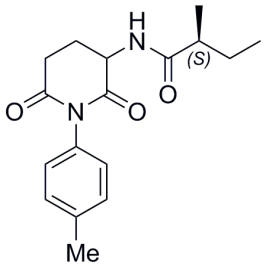
Obtained using procedure D, on 0.283 mmol scale; yield 77% (0.218 mmol, 82.4 mg). Purification with column chromatography (PE : EA [0 to 100% EtOAc in PE]); white solid, mp 124 – 126 °C. ^{1}H NMR (500 MHz, $CDCl_3$, combined) δ 7.57 – 7.50 (m, 4H), 7.45 – 7.39 (m, 4H), 7.35 – 7.32 (m, 1H), 6.44 – 6.41 (m, 1H), 4.98 (ABq, *J* = 14.0 Hz, 2H), 4.59 (dt, *J* = 12.9, 5.3 Hz, 1H), 2.90-2.75 (m, 2H), 2.54 – 2.49 (m, 1H), 2.21 (ddd, *J* = 14.2, 6.9, 2.7 Hz, 1H), 1.79 - 1.65 (m, 2H), 1.49 – 1.44 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 0.92 (dt, *J* = 16.0, 7.4 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$, combined) δ 176.7, 176.6, 172.0, 171.9, 171.1, 140.6, 140.5, 135.6, 129.0, 128.7, 127.3, 127.1, 127.0, 51.3, 51.2, 43.4, 42.80, 31.7, 27.3, 27.1, 24.3, 24.2, 17.2, 11.8, 11.7. MS (ESI): *m/z* calcd for $C_{23}H_{26}N_2O_3$ $[M]^+$:378.19; found 379.27; found $[M+Na]^+$: 401.25; found $[M+K]^+$: 417.19, HRMS (ESI): *m/z* calcd for $C_{23}H_{27}O_3N_2$ $[M+H]^+$:379.20162; found 379.20163.

(2*S*)-N-(1-(4-cyanobenzyl)-2,6-dioxopiperidin-3-yl)-2-methylbutanamide (11d)



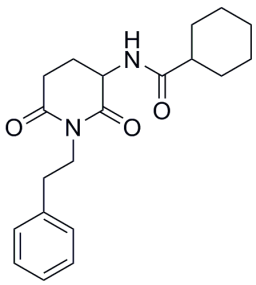
Obtained using procedure D, on 0.347 mmol scale; yield 70% (0.243 mmol, 79.4 mg). Purification with column chromatography (PE : EA [0 to 100% EtOAc in PE]); white solid, mp 132 – 133 °C. ^{1}H NMR (500 MHz, $CDCl_3$, combined) δ 7.58 (d, *J* = 7.9 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 6.28 (b, 1H), 4.97 (ABq, *J* = 14.0 Hz, 2H), 4.60 – 4.55 (m, 1H), 2.95 – 2.75 (m, 2H), 2.54- 2.52 (m, 1H), 2.20 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.70 – 1.61 (m, 1H), 1.49-1.32 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.91 (dt, *J* = 14.8, 7.4 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$, combined) δ 176.8, 176.7, 171.9, 171.0, 141.8, 132.3, 129.3, 118.5, 111.5, 51.2, 43.3, 42.9, 42.8, 31.7, 27.3, 27.1, 24.3, 24.2, 17.2 11.8, 11.7. MS (ESI): *m/z* calcd for $C_{18}H_{21}N_3O_3$ $[M]^+$:327.16; found 328.17; found $[M+Na]^+$: 350.22; found $[M+K]^+$: 366.16**,** HRMS (ESI): *m/z* calcd for $C_{18}H_{22}O_3N_3$ $[M+H]^+$: 328.16557 ; found 328.1655.

(2*S*)-N-(2,6-dioxo-1-(p-tolyl)piperidin-3-yl)-2-methylbutanamide (12d)



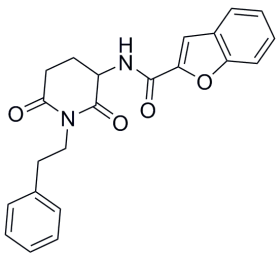
Obtained using procedure D, on 0.11 mmol scale; yield 82% (0.09 mmol, 27.2 mg). Purification with column chromatography (PE:EA [0 to 100% EtOAc in PE]); yellow semi-solid.^{1}H NMR (500 MHz, $CDCl_3$, combined) δ 7.27 (d, *J* = 6.8 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.35 (dd, *J* = 8.1, 5.9 Hz, 1H), 4.75 (dt, *J* = 12.7, 6.3 Hz, 1H), 3.03 – 2.90 (m, 2H), 2.66 – 2.62 (m, 1H), 2.39 (s, 3H), 2.24 – 2.19 (m, 1H), 1.96 – 1.93 (m, 1H), 1.71 – 1.65 (m, 1H), 1.50 – 1.45 (m, 1H), 1.16 (dd, *J* = 6.7, 3.1 Hz, 3H), 0.92 (dd, *J* = 12.1, 7.3 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$, combined) δ 176.9, 172.2, 171.3, 138.9, 132.0, 130.1, 127.8, 51.5, 51.4, 42.9, 32.0, 27.3, 27.2, 24.5, 21.2, 17.3, 11.8. MS (ESI): *m/z* calcd for $C_{17}H_{22}N_2O_3$ $[M]^+$:302.16; found 303.22; found $[M-H]^+$: 301.20; found $[M+Na]^+$: 325.20; found $[M+K]^+$: 341.15**,** HRMS (ESI): *m/z* calcd for $C_{17}H_{23}O_3N_2$ $[M+H]^+$: 303.17032; found 303.17023.

(N-(2,6-dioxo-1-phenethylpiperidin-3-yl)cyclohexanecarboxamide (13d)



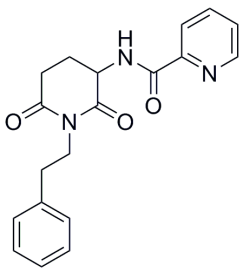
Obtained using procedure D, on 0.147 mmol scale; yield 90 % (0.132 mmol, 45.2 mg). Purification with column chromatography (PE: EA [0 to 100% EtOAc in PE]); white solid, mp 156–158 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 7.22 – 7.20 (m, 3H), 6.30 (d, *J* = 5.1 Hz, 1H), 4.45 (dt, *J* = 12.9, 5.2 Hz, 1H), 4.06 – 3.93 (m, 2H), 2.84 – 2.77 (m, 3H), 2.74 – 2.66 (m, 1H), 2.51 (dtd, *J* = 12.6, 5.2, 2.3 Hz, 1H), 2.17 (ddd, *J* = 11.6, 7.6, 3.5 Hz, 1H), 1.90 (t, *J* = 14.7 Hz, 2H), 1.84 – 1.77 (m, 2H), 1.71 – 1.61 (m, 2H), 1.49 – 1.40 (m, 2H), 1.31 – 1.23 (m, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 171.9, 170.9, 138.0, 128.9, 128.4, 126.5, 51.1, 45.2, 41.5, 41.3, 33.9, 31.6, 29.5, 29.4, 25.6, 24.4, 24.3. MS (ESI): *m/z* calcd for $C_{20}H_{26}N_2O_3$ $[M]^+$: 342.19; found 343.29; found $[M+Na]^+$: 365.28; found $[M+K]^+$: 381.22**,** HRMS (ESI): *m/z* calcd for $C_{20}H_{27}O_3N_2$ $[M+H]^+$:343.20162; found 343.20142.

N-(2,6-dioxo-1-phenethylpiperidin-3-yl)benzofuran-2-carboxamide (14d)



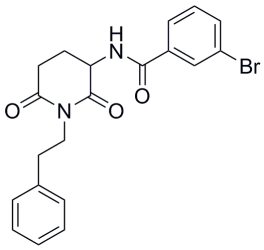
Obtained using procedure D, on 0.12 mmol scale; yield 89 % (0.107 mmol, 40 mg). Purification with column chromatography (PE:EA [0 to 100% EtOAc in PE]); pink solid, mp 155 – 156 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.67 (m, 1H), 7.56 – 7.51 (m, 2H), 7.49 – 7.42 (m, 2H), 7.32 – 7.19 (m, 3H), 7.26 – 7.21 (m, 3H), 4.69 (dt, *J* = 12.9, 5.4 Hz, 1H), 4.14 – 4.00 (m, 2H), 2.91 – 2.84 (m, 3H), 2.79 (td, *J* = 13.1, 6.7 Hz, 1H), 2.69 – 2.63 (m, 1H), 1.85 (qd, *J* = 13.1, 4.9 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 170.7, 158.9, 154.8, 147.8, 138.0, 128.9, 128.8, 128.4, 127.4, 127.2, 126.6, 123.8, 122.8, 111.8, 111.1, 51.3, 41.7, 33.9, 31.6, 24.3. MS (ESI): *m/z* calcd for $C_{22}H_{20}N_2O_4$ $[M]^+$:376.14; found 377.19; found $[M-H]^+$: 375.17; found $[M+Na]^+$: 399.18; found $[M+K]^+$: 415.18, HRMS (ESI): *m/z* calcd for $C_{22}H_{21}O_4N_2$ $[M+H]^+$: 377.14958; found 377.14957.

N-(2,6-dioxo-1-phenethylpiperidin-3-yl)picolinamide (15d)



Obtained using procedure D, on 0.14 mmol scale; yield 85 % (0.119 mmol, 40 mg). Purification with column chromatography (PE:EA [0 to 100 % EtOAc in PE]); yellow semi- solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 5.9 Hz, 1H), 8.63 (d, *J* = 3.7 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 7.89 (t, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 6.5, 5.3 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.25 (dd, *J* = 14.8, 7.2 Hz, 3H), 4.76 – 4.72 (m, 1H), 4.10 – 4.02 (m, 2H), 2.93 – 2.77 (m, 4H), 2.62 – 2.59 (m, 1H), 1.92 (qd, *J* = 13.1, 4.8 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 170.9, 164.6, 149.1, 148.3, 138.1, 137.3, 128.9, 128.4, 126.6, 126.5, 122.2, 51.3, 41.7, 33.9, 31.7, 24.3. MS (ESI): *m/z* calcd for $C_{19}H_{19}N_3O_3$ $[M]^+$:337.14; found $[M-H]^+$:336.17; found $[M+Na]^+$: 360.17**,** HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_3N_3$ $[M+H]^+$: 338.14992; found 338.1499.

3-bromo-N-(2,6-dioxo-1-phenethylpiperidin-3-yl)benzamide (16d)



Obtained using procedure D, on 0.036 mmol scale; yield 90% (0.033 mmol, 13.4 mg). Purification with column chromatography (PE:EA [0 to 100% EtOAc in PE]); white solid, mp 166-168°C, [α]= +13.57 (c= 0.84, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (t, *J* = 1.6 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.23 (t, *J* = 6.8 Hz, 3H), 7.01 (d, *J* = 4.8 Hz, 1H), 4.62 (dt, *J* = 12.9, 5.0 Hz, 1H), 4.11 – 4.00 (m, 2H), 2.91 – 2.84 (m, 3H), 2.81 – 2.74 (m, 1H), 2.71 – 2.66 (m, 1H), 1.78 (qd, *J* = 13.1, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 170.8, 166.1, 138.0, 135.4, 135.0, 130.3, 130.2, 129.0, 128.5, 126.7, 125.6, 122.9, 52.0, 41.7, 33.9, 31.6, 24.3.MS (ESI): *m/z* calcd for $C_{20}H_{19}BrN_2O_3$ $[M]^+$: 414.06; found $[M+H]^+$: 415.18; found $[M+Na]^+$:437.15**,** HRMS (ESI): *m/z* calcd for $C_{20}H_{20}O_3N_2Br$ $[M+H]^+$: 415.06518; found 415.06522.

Crystal X ray structure determination

X-ray diffraction data for single crystal of compound **3c-ii** was collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus CuKα radiation source (λ = 1.5418 Å). Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments, performed at 130 K. The obtained data set was processed with CrysAlisPro software.[S8] The phase problem was solved by direct methods using SUPERFLIP.[S9] Parameters of obtained models were refined by full-matrix least-squares on F^2 using SHELXL-2014/6. [S10] Calculations were performed using WinGX integrated system (ver. 2014.1).[S11] Figure was prepared with Mercury 3.7 software. [S12]

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter U_{iso}[H] = 1.2 (or 1.5 (methyl groups only)) U_{eq}[C]. Crystal data and structure refinement results for presented crystal structure are shown in Table S1. The molecular geometry (asymmetric unit) observed in the crystal structure is shown in Figure S1.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1590022. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

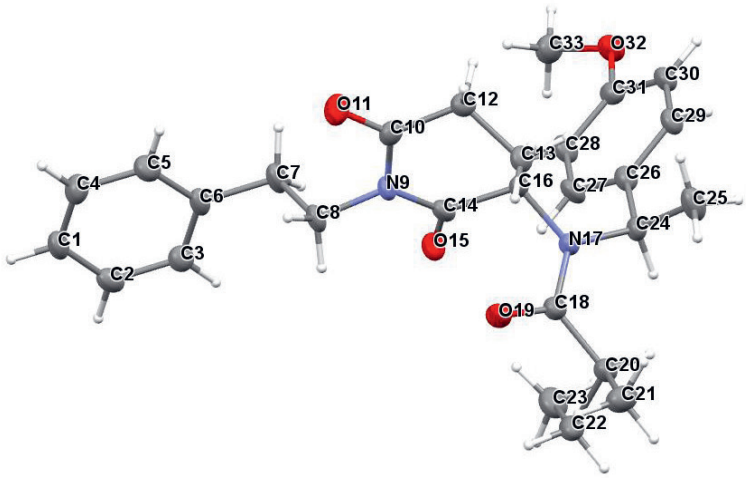


Figure S1. Molecular geometry observed in the crystal structures of compound **3c-ii** (asymmetric unit), showing the atom labelling scheme. Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.

Table S1. Crystal data and structure refinement results for compound **3c-ii.**

	3c-ii
Empirical moiety formula	$C_{27}\,H_{34}\,N_2\,O_4$
Formula weight [g/mol]	450.56
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unite cell dimensions	a = 7.8214(2)Å b = 13.0831(5)Å c = 23.4531(10)Å α=b=g=90
Volume [Å^3]	2399.91(15)
Z	4
D_{calc} [Mg/m^3]	1.247
μ [mm^{-1}]	0.669
F(000)	968
Crystal size [mm^3]	0.2 x 0.05 x 0.05
Θ range	11.65° to 70.60°
Index ranges	-8 ≤ h ≤ 9, -14 ≤ k ≤ 15, -28 ≤ l ≤ 23
Refl. collected	6274
Independent reflections	4023 [R(int) = 0.0744]
Completeness [%] to Θ	95.12 (Θ 66.9°)
Absorption correction	Multi-scan
Tmin. and Tmax.	0.841 and 1.000
Data/ restraints/parameters	402 / 0 / 303
GooF on F2	1.096
Final R indices [I>2sigma(I)]	R1= 0.0787, wR2= 0.0787
R indices (all data)	R1= 0.0865, wR2= 0.1144
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e•Å^{-3}]	0.16 and -0.19

REFERENCES

[s1] A. Ohashi, A. Satake, Y. Kobuke, Y. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 365 – 374.

[s2] P.M. Gannett, D.L. Nagel, P.J. Reilly, T. Lawson, J. Sharpe, B. Toth, *J. Org. Chem.* **1988**, *53*, 1064 – 1071.

[s3] A.L. Gutman, A. Boltanski, *J. Chem. Soc. Perkin Trans. 1*, **1989**, *0*, 47 – 49.

[s4] T. Nakano, C. Djerassi, R.A. Corral, O.O. Orazi, *J. Org. Chem.* **1961**, *26*, 1184 – 1191.

[s5] P.S. Barbosa, A. S. Abreu, E. F. Batista, G.M.S.P. Guilhon, A. H. Müller, M.S.P. Arruda, L.S. Santos, A.C. Arruda, R.S. Secco, *Biochem. Syst. Ecol.* **2007**, *35*, 887 – 890.

[s6] B. Teng, J. Zheng, H. Huang, P. Huang, *Chin. J. Chem.* **2011**, *29*, 1312 – 1318.

[s7] B. Ndunda, M.K. Langat, J.M. Wanjohi, J.O. Midiwo, L.O. Kerubo, *Planta Med.* **2013**, *79*, 1762 – 1766.

[s8] Rigaku-Oxford Diffraction; CrysAlisPro Oxford Diffraction Ltd, Abingdon, England V 1. 171. 36. 2.(release 27-06-2012 CN (**2006**).

[s9] L. Palatinus, G. Chapuis, *J. Appl. Cryst.* **2007**, *40*, 786 – 790.

[s10] G.M. Sheldrick, *ActaCryst.* **2008**, *A64*, 112 – 122.

[s11] L. Farrugia, *J. J. Appl. Cryst.* **1999**, *32*, 837 – 838.

[s12] C. F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J. van de Streek, *J. Appl. Cryst.* **2006**, *39*, 453 – 457.